ANNUAL REVIEW OF MEDICINE

WINDSOR C. CUTTING, *Editor*
Stanford University School of Medicine

HENRY W. NEWMAN, *Associate Editor*
Stanford University School of Medicine

VOLUME 5

1954

PREFACE

Books come of age somewhat sooner than men, and at five years one may assess something of the useful maturity of the *Annual Review of Medicine.* The editors had as their initial goal the periodic review of more or less all of medicine, presented so as to be interesting to an intelligent physician of almost any special persuasion.

The first part of this goal has become somewhat more confined in that the generic chapter headings have come often to have subtitles partially limiting their scope. The authors now are requested to write in some detail on that portion of the general field they know best, and to review briefly only the salient advances in the rest of the field. The feeling is that this lends inspiration to the writing, and to the reading, and that next year's author will fill in the details in another segment.

The second portion of the goal has been less consistently handled. Some of the chapters have been superbly written at the desired level; in short, both editors read them with pleasure. Others have been somewhat more technical and may have failed of the goal of general interest. But, the precedent has been firmly set and the color of the articles, like the color of the volumes, is becoming common knowledge.

All told, the editors feel that at least a moderate service has been made to the insatiable problem of current literature.
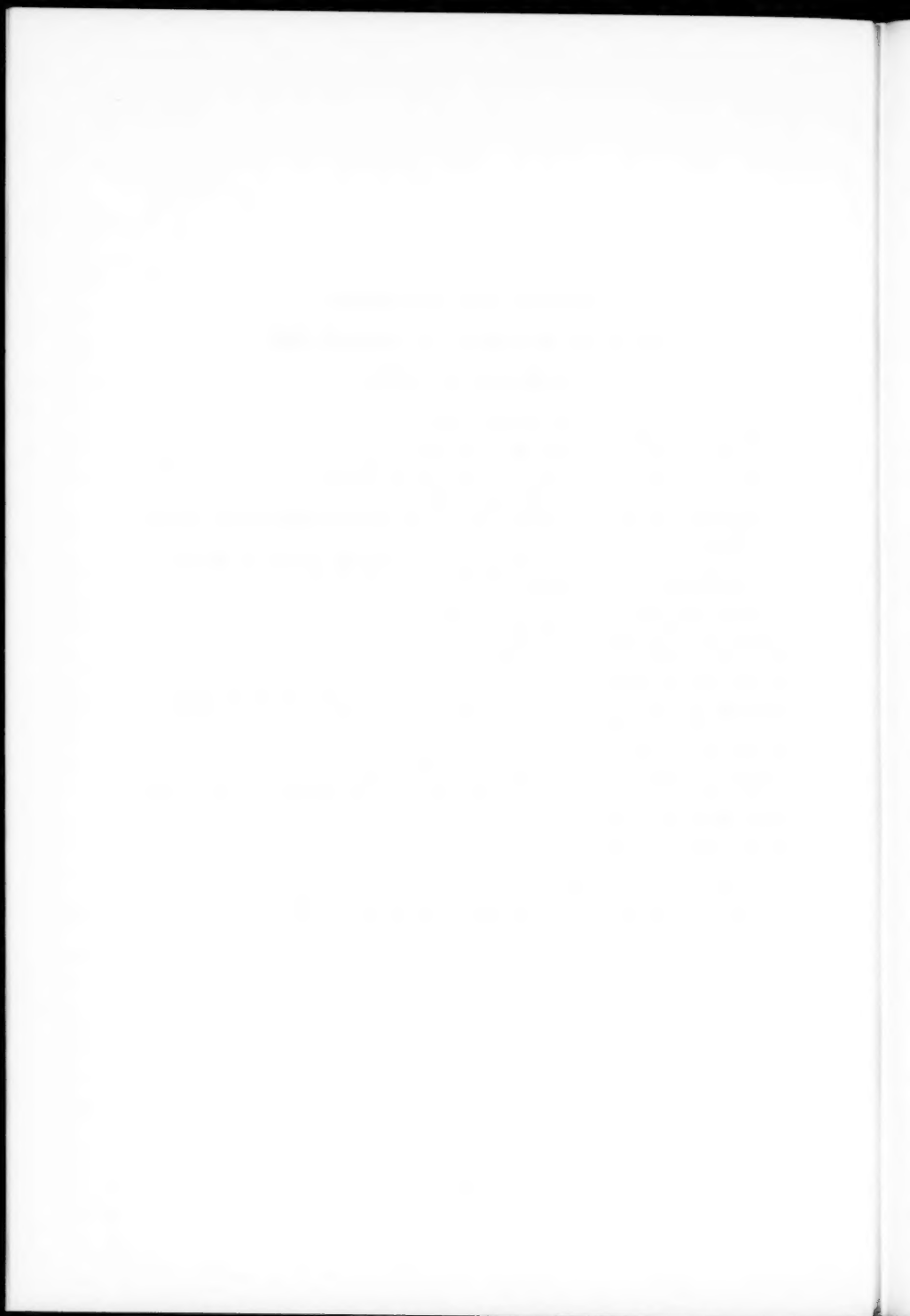
Once again, we are more than grateful for the patient help of Miss Bea Morrow and her confreres in the Editor's Office.

J.S.L.B.	R.M.
K.S.G.	S.C.M.
C.G.L.	H.W.N.

W.C.C.

TOPICS AND AUTHORS
ANNUAL REVIEW OF MEDICINE
VOLUME 6 (1955)

CONTENTS

ix

INFECTIOUS DISEASES: PROBLEMS OF ANTIMICROBIAL THERAPY[1]

By Ernest Jawetz

University of California Medical Center, San Francisco 22, California

Many physicians associate the word "infection" with the term "antibiotic." In the short span of a few years the impact of antimicrobial therapy has greatly altered the practice of medicine. Sulfonamides and antibiotics have saved innumerable lives and have made possible technical procedures in medicine and surgery not feasible previously. However, they have not eliminated the role of microorganisms in the causation of disease and they have introduced new problems in medical management. The microbial world has responded to the introduction of antimicrobial substances into its ecological balance with derangement of normal bacterial flora, development of resistance, and disturbances in host-parasite relationship. It has become increasingly apparent that the indiscriminate use of antimicrobial drugs by physicians everywhere has vitiated their benefits. The action of an antimicrobial drug in man is quite different from the effect of that same drug on a specific microorganism in a test tube. The interplay between drug, host, and microbial world is being re-emphasized by recent events. This review attempts to summarize certain developments in the realm of antimicrobial therapy. Only very few of these can be classified as "advances" in therapy. The majority represent recognition of certain broad biological principles, the violation of which often leads to trouble. A section at the end of this review deals with selected other recent developments in infectious diseases.

Attitudes and Trends Affecting "New" Drugs

The search for new, better, more widely applicable drugs has been intensified in the past few years. The inevitable large sales of any new antimicrobial agent provide for considerable financial reward if one considers that hundreds of tons of the accepted antibiotics are produced and sold each year. A regular trend has characterized the attitudes of physicians and laity alike, which is shown diagrammatically in Fig. 1. The initial reaction to a product which promises clinical usefulness is a "phase of enthusiasm" which soon reaches a high peak. Great things are expected of the new agent, but little is known. As laboratory studies progress and a few patients are treated by disinterested and objective physicians, the "phase of initial stabilization" is reached. Certain limitations of the agent and some of its disadvantages become manifest. Later, after a variable length of time, the new drug is found to cause serious side effects. Although the toxic manifestations may be rare, the preparation abruptly loses popularity; everyone talks only of its harmful effects, not of its continued usefulness. This might be

[1] The survey of literature pertaining to this review was completed in June, 1953.
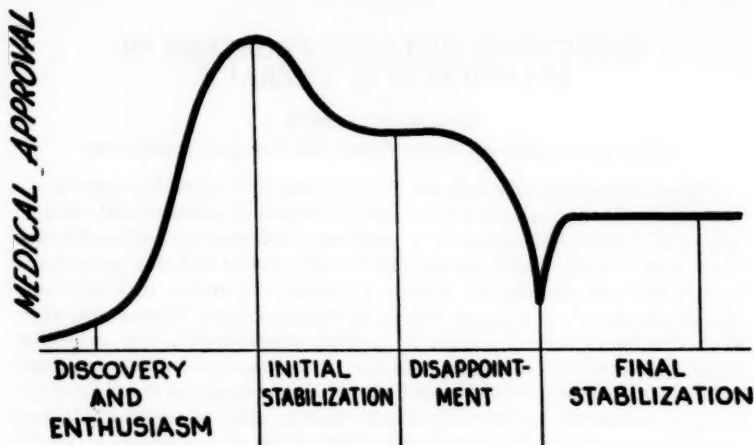
FIG. 1. Phases in the Establishment of a New Drug.

called the "phase of disappointment." Finally some sort of balance is reached between the real usefulness and the potential harm of the drug, and a tentative, rational place in the medical armamentarium can be assigned to it, the "phase of final stabilization." To a greater or lesser extent all the newer drugs have passed through these phases, and it seems reasonable to assume that the trend will continue. Awareness of this pattern of response will permit the physician to evaluate a new agent according to the successive phases and to avoid unwarranted optimism or undue disappointment.

Indiscriminate Use of Antibiotics and Harmful Effects

Antibiotics are among the most widely used therapeutic agents in practical medicine; they also are the most pre-eminently misused group of drugs. In the United States (1) the yearly output of penicillin is now about 360 tons and of streptomycin, 250 tons; in 1952 the combined production of chlortetracycline (Aureomycin) chloramphenicol (Chloromycetin), and oxytetracycline (Terramycin) approached 300 tons. If one assumes that the bulk of these drugs is administered to patients, it becomes at once apparent how colossal the waste must be. Conservatively estimated, 1 to 5 per cent of all antimicrobial drugs are administered on proper clinical indication. The rest is wasted in the following ways: (a) In minor respiratory illnesses which are ordinarily viral in origin and not benefited; (b) For unreasonable and largely hypothetical "prophylaxis" of bacterial infections; (c) In unnecessary combinations of drugs. This imposes not only a quite unnecessary stress on the patient's pocketbook, but also has resulted in definite harmful effects.

Among the more important results of the indiscriminate large-scale use

of antibiotics are widespread hypersensitivity in the population, direct toxic effects, alteration of bacterial flora with serious "superinfection," and rapid emergence of bacterial resistance. These aspects will be reviewed briefly because increased familiarity with these problems is essential if antibiotics are to be employed rationally and effectively.

Hypersensitivity and direct toxicity. The clinical symptoms and signs resulting from either hypersensitivity of the patient or from direct toxicity of the drug cannot always be differentiated. The various manifestations (cutaneous, oral, gastrointestinal, nervous, or hematopoietic) have been reviewed authoritatively by Finland & Weinstein (2). Skin eruptions, fever, nausea, and vomiting occur so frequently during antibiotic administration that the physician must ask himself constantly whether they are manifestations of the underlying illness or reactions to the drug. Fortunately, most side effects are transient and subside spontaneously when the offending agent is withdrawn.

Even penicillin, that most ideal of antibiotics (and most widely misused) can give rise to side effects, although most of them, such as urticaria, are relatively unimportant. Direct toxicity of purified penicillin G is indeed negligible since four pounds of the drug (100 million units daily) have been given in one month to a patient without difficulty [Jawetz (3)].

With the administration of penicillin to many millions of people, however, serious hypersensitivity reactions, anaphylaxis, and death, have been reported (4 to 10). Since the majority of patients who developed serious anaphylactic reactions had some past history of allergies, or of minor reactions to penicillin, it must be urged that physicians inquire about such past reactions before injecting penicillin. In persons suspected of being hypersensitive, skin tests with diluted penicillin often give an immediate wheal-type reaction (9, 10). Individuals with positive skin tests should receive penicillin only with greatest precautions (available epinephrine, aminophylline, close observations for one hour, antihistaminics) or not at all.

Although persons sensitive to penicillin G might tolerate penicillin O, cross reactions are frequent (10, 11). Among the variety of major allergic reactions to penicillin, Loeffler's syndrome (12), periarteritis nodosa (13), purpura, and nephritis (14) have been encountered. Whereas allergic reactions to penicillin are frequent, Herxheimer reactions in vascular syphilis have been encountered only very rarely (15), although they were much discussed and feared in the early days of penicillin treatment of syphilis. During massive penicillin therapy occasional false positive tests for protein and sugar in the urine can be attributed directly to high concentrations of penicillin in the urine, and are entirely harmless [Whipple & Bloom (16)].

Chlortetracycline or oxytetracycline also occasionally produce reactions of the anaphylactic type (17). Much more frequent, particularly with high doses, are the gastro-intestinal upsets, characterized by nausea, vomiting, diarrhea, and perineal pruritus. It is not precisely understood to what extent these side effects can be attributed to direct local irritation, to allergy, and

to changes in microbial flora [Merliss & Hoffman (18)]. Considering the isomorphism of oxytetracycline and chlortetracycline hydrochlorides, it is surprising that a given person may tolerate one, but not the other of these drugs (19).

The effect of chlortetracycline on the liver remains undetermined. Experiments have shown that it will prevent dietary injury to the liver in rats (20). In man, according to Lepper, *et al.* (21) and Rutenberg & Pinkes (22), large doses of chlortetracycline result in disturbances of hepatic function, as measured by laboratory tests. The intestinal flora was found to be appreciably suppressed after intravenous injection of chlortetracycline (23). This phenomenon suggested that chlortetracycline was excreted in the bile and that the jaundice produced by large parenteral doses might be attributed to competition of the drug with bile for excretion by the liver and kidneys (24). In seriously ill persons with impaired liver and kidney function, large doses of terramycin resulted in a sharp increase in nitrogen retention and in death in a shock-like state [Bateman, *et al.* (25)]. This effect was ascribed to cumulation of the drug, which since it was no longer excreted, built up to toxic levels.

The toxicity of streptomycin for the vestibular apparatus has made its protracted use hazardous. The advent of dihydrostreptomycin was welcomed with the hope that it would be less prone to cause serious neurotoxicity. Unfortunately dihydrostreptomycin may cause deafness upon prolonged administration (26). Particularly when administered intrathecally, the incidence of deafness with dihydrostreptomycin is so severe that only streptomycin should be administered by this route [Welch (27)]. Despite occasional severe reactions simulating transverse myelitis with shock, subsequent intrathecal doses of streptomycin may be well tolerated (28). Recently a significant improvement in streptomycin therapy was announced [Heck & Hinshaw (29)]. Whereas the injection of one gram streptomycin daily for 120 days resulted in vestibular toxicity in 18 per cent of patients, the mixture of 0.5 gram streptomycin with 0.5 gram dihydrostreptomycin injected daily for 120 days in 42 patients, gave no noticeable toxicity. Since the antimicrobial effects, but not the toxic manifestations, of the two forms of streptomycin are identical, the administration of such a mixture may have advantages for protracted therapy. On the other hand, simultaneous use of streptomycin and dihydrostreptomycin carries the risk of sensitization to both forms. It may be unnecessary to resort to such mixtures since the administration of one gram of either form every third day has good therapeutic efficacy in combined therapy and minimizes toxic side effects.

When chloramphenicol was first introduced the presence of a nitrobenzene ring in the chloramphenicol molecule suggested possible toxicity for the bone marrow. When early clinical studies failed to support this possibility, the drug was administered with complete abandon and on a vast scale to millions of patients. The earliest reports on depression of hematopoiesis by chloramphenicol went almost unnoticed [Volini, *et al.* (30)]. Subsequently,

after a number of more or less well-documented instances of aplastic anemia were published, medical opinion suddenly turned (31, 32). Whereas chloramphenicol had been prescribed quite indiscriminately and without specific indications, now physicians hesitated to use this agent even when it was clearly the drug of choice. Both types of behavior were based on emotion rather than on sound reason. When the evidence was examined in a sober frame of mind [Lewis, *et al.* (33)] only 55 cases of blood dyscrasia could be attributed with certainty to chloramphenicol. Of these, 44 had aplastic anemia and 23 terminated fatally. Among 143 patients receiving a variety of drugs including chloramphenicol, there were 95 cases of aplastic anemia. In 341 other cases of blood dyscrasia of whom 157 had aplastic anemia, chloramphenicol had definitely not been taken. These facts clearly indicate that the specific danger of chloramphenicol had been exaggerated. Chloramphenicol, or any other antimicrobial agent, should be administered when it is indicated, but only then. The indiscriminate, thoughtless, casual dispensing of these invaluable agents as if they were placebos must be strongly condemned.

Alteration in microbial flora.—Weinstein (34) and Appelbaum & Leff (35) observed early in the "antibiotic era" that new bacterial infections occurred spontaneously during the course of antibiotic treatment. These "superinfections" were attributable to microorganisms which were not affected by the drug administered and gained dominance as the normal microbial flora was suppressed. In recent years, with the increasing use of broad spectrum antibiotics, the principal offenders in causing "superinfections" have been *Proteus*, *Pseudomonas*, staphylococci and yeasts. The first two of these are regular inhabitants of the intestinal tract, and are not infrequently found on the skin, in air, and in water. Normally they are present in small numbers, cause invasive infection only rarely, and are "opportunists," rather than true pathogens [Yow (36), Waisbren (37), Jawetz (38)]. When the normal flora is suppressed by antibiotics, *Proteus* and *Pseudomonas*, which are naturally resistant to most antimicrobial drugs, quickly increase in numbers, particularly in the antibiotic-laden environment of hospitals. Under the title "Hospital Infection" an editorial commented that "*Pseudomonas* has established itself as a secondary invader of burns and discharging ears and is becoming a common cause of urinary tract infection in hospitals" (39, 40).

In addition, these organisms occasionally are introduced into the meninges through trauma or spinal anesthesia and set up an indolent meningitis which is difficult to eradicate (38, 41). It often necessitates the intrathecal injection of selected drugs, such as polymyxin B or neomycin.

Pigment producing chromobacteria, which inhabit water and air and ordinarily are considered nonpathogenic, occasionally establish themselves in the urological operating room. They contaminate instruments and solutions, can be introduced into the urinary tract, cause infection, and may enter the bloodstream with fatal results [Wheat, *et al.* (42)].

In the course of oxytetracycline treatment of bacterial pneumonia, staphylococcal superinfections of lung and gastrointestinal tract were ob-

served. Severe, and occasionally fatal enteritis and colitis associated with staphylococci has occurred in a number of patients treated with the "broad spectrum antibiotics" (43 to 46). Dearing & Heilman (47) suggest that the broad spectrum antibiotics suppress the normal flora and permit the establishment of resistant staphylococci in the intestinal tract. Toxins produced by these staphylococci are incriminated in producing functional disturbances and lesions. Recommended therapy consists of withdrawing the offending antibiotic and administering another agent, e.g., erythromycin, to suppress the staphylococci in the intestine.

Everyone carries a few *Monilia* and other yeasts in the mouth, in the intestinal tract, and on the skin. During therapy with chlortetracycline, chloramphenicol, or oxytetracycline, yeasts increase greatly in number and are often associated with abnormalities of the mucous membranes (48, 49, 50). This "rise of the yeasts" during antibiotic administration has been noted quite generally. The pathogenic potential of these fungi has caused concern, although Kligman (51) minimized the danger and considered the overgrowth of yeasts mainly a saprophytic surface phenomenon. Brown *et al.* (52) however, reported fatal infections following therapy with broad spectrum antibiotics, and demonstrated invasion of the blood stream by yeasts and focal suppuration in many organs. The regularity with which the yeast flora increases under the influence of chlortetracycline has led to experiments directed at the underlying mechanism. Under certain conditions, aureomycin can stimulate the growth of *Candida* and other yeasts in the test tube (53, 54), and markedly increase their virulence for mice (55, 56). In man it is uncertain whether the antibiotic directly enhances the growth of yeast, or whether, by eliminating bacteria, removes a normal restraint [Paine (57)]. The search for substances which are systemically effective against yeasts has not yet yielded useful results, although undecylenic acid or parahydroxybenzoic acid taken orally, has been claimed to suppress their growth (50, 58).

These examples illustrate the delicate balance in the normal microbial flora of the human body, and the dangers of disturbing it. The physician must ask himself whether administration of an antibiotic will help his patient sufficiently to offset the potential additional difficulties it may create.

Rising bacterial resistance to antibiotics.—The problems created for both the individual and the community by the large scale indiscriminate use of antibiotics are most serious in the field of increasing bacterial resistance. A decade ago when penicillin first came into general use, most staphylococci were quite sensitive to the drug. In subsequent years almost every patient who entered a hospital received penicillin for one reason or another. As a result, penicillin-sensitive staphylococci were eliminated from the hospital environment; by 1948, about three-fourths of all staphylococcal strains derived from hospital patients or attendants were resistant to penicillin, by virtue of producing penicillinase, an enzyme destroying penicillin (59). Needham & Nichols (60) compared the antibiotic resistance of staphylococci from 1949 to 1951. In hospitalized patients from 44 to 68 per cent of staphy-

lococci were penicillin-resistant, about 40 per cent were streptomycin-resistant, throughout the period of observation. Whereas all strains were sensitive to chlortetracycline in 1949, 40 per cent were resistant to it and oxytetracycline in November, 1951. In addition to selection of resistant variants by drug treatment, cross-infection plays an important role in disseminating the resistant strains in a hospital population. Clarke *et al.* (61) who correlated cultures from ward air, dust, and the respiratory tract of patients, discovered the highest incidence of resistant staphylococci in surgical wards where the most antibiotic treatment was given. A fatal case of staphylococcus septicemia confirmed that these organisms likewise resisted all antibiotics *in vivo*.

A hopeful note was sounded by Sherris & Florey's (62) experience in England, staphylococci from acute closed infection and deep-seated processes were mostly penicillin-sensitive, whereas penicillin-resistant staphylococci were associated with superficial wounds. In contrast, Finland & Haight (63) at the Boston City Hospital, found among 500 strains of coagulase-positive hemolytic staphylococci, 75 per cent resistant to penicillin and about one-third resistant to chlortetracycline and oxytetracycline. Resistant strains came with equal frequency from closed deep lesions as sensitive ones. Others (64, 65, 66) had similar experiences. All kinds of staphylococci, including those from deep and closed processes, tended to be highly penicillin-resistant. Thus sensitivity testing remained the only true criterion of drug selection.

The problem of drug resistance might be simplified if micro-organisms developed resistance to only one drug at one time. Unfortunately, almost complete cross-resistance exists between chlortetracycline and oxytetracycline (67 to 70), and between erythromycin and carbomycin (71); partial cross-resistance exists between neomycin and streptomycin (72), and between chloramphenicol and chlortetracycline or oxytetracycline (69). Curiously enough, increased resistance to chlortetracycline, oxytetracycline, or chloramphenicol, is often associated with increased susceptibility to streptomycin, and vice versa (68 to 70). Kaipanen (68), therefore, proposed the simultaneous use of drugs giving separate resistance patterns, e.g., chlortetracycline-streptomycin, to minimize development of microbial resistance.

Welch *et al.* (73), using 185 children as subjects, studied the prolonged use of tooth powder containing 500 units of penicillin per gram. One hundred seventy-eight children in the same institution served as controls. After a three-year period, the penicillin users showed higher total counts of oral bacteria and a significantly greater number of penicillin-resistant staphylococci, streptococci, and *Neisseriae* than the controls. Thus, the use of any dentrifice containing penicillin can hardly be recommended.

Gram-positive cocci have not been the only ones to increase markedly in antibiotic resistance. Scheierson (74) found that gram-negative bacilli, particularly coliform organisms from urinary tract infections, showed significant increases in resistance to aureomycin in three years. Resistance to chloramphenicol has not developed to the same degree.

New Antimicrobial Agents

The problems posed by the steady rise in microbial resistance to established antibiotics has intensified the search for powerful new drugs. In spite of great efforts by drug manufacturers, no satisfactory answers have been found.

Two new antibiotics, erythromycin and carbomycin, were announced with considerable fanfare. Both agents are principally effective against gram-positive cocci (75, 76). Their spectrum *in vitro* is virtually identical, although from three to six times greater concentrations of carbomycin are needed for inhibition of test organisms (77, 78). Both drugs permit the rapid emergence of resistant variants, and the cross-resistance between them is almost complete (78, 79). Development of resistance is greatly delayed in the presence of either streptomycin or penicillin (79). Serum levels of the drugs are relatively low following oral administration (80). Kirby *et al.* (81) report much higher serum levels of erythromycin following oral administration in acid-resistant tablets.

The potential usefulness of these new drugs is greatest in penicillin-resistant staphylococcal infection. Although published clinical evidence does not permit final judgment, personal experience suggests that in major infections with blood stream invasion, in bacterial endocarditis, etc., these drugs are rarely helpful, because staphylococci quickly become resistant. Perhaps a useful application of these drugs may lie in antibiotic combinations.

Two new types of penicillin also deserve brief mention. Jensen *et al.* (82) prepared the hydriodide of the diethylaminoethylester of penicillin G and observed that it acted as a repository penicillin and also appeared in higher concentration in the lungs, than did other penicillins. Clinical results in pulmonary infections were favorable. These conclusions were confirmed by Grigsby *et al.* (83) who re-investigated the preparation (Neo-Penil). Subsequently, however, severe anaphylactoid and fatal reactions to Neo-Penil were reported and the Council on Pharmacy and Chemistry of the American Medical Association issued a warning against the use of the preparation (84).

Elias *et al.* (85) prepared dibenzylethylenediamine penicillin as a new repository form, which resulted in exceedingly prolonged low blood levels. While of uncertain usefulness in the treatment of established infections, these low drug levels persisting for weeks after an injection would appear uniquely suited for the prevention of infections attributable to penicillin-sensitive organisms. Stollermann & Rusoff (86) feel that this might be a good preparation for the prophylaxis of hemolytic streptococcus infection in rheumatic children. A single intramuscular injection every two to three weeks may suffice.

Combined Antibiotic Therapy

The apparently reasonable idea that "if one antibiotic is good, two should be better," has led to the administration of vast amounts of antimicrobial drugs in combinations. It came as a shock to many physicians when it

was demonstrated that one drug might actually diminish the effectiveness of another agent. The consternation increased when this phenomenon of antagonism occurred not only *in vitro*, but in experimental animals as well (87, 88). Lepper & Dowling (89) found that patients with pneumococcus meningitis had a much higher mortality when treated with a combination of chlortetracycline and penicillin, than with penicillin alone. Public concern reached a high pitch (90). Physicians joined the "antagonism" or the "no-antagonism" camp with a good deal of emotion. Jawetz & Gunnison (91, 92) summarized the experimental basis for combined antibiotic action, in an effort to clarify the highly charged atmosphere. They showed that experimental antibiotic antagonism occurred only under very special circumstances: (*a*) the antagonizing drug (chlortetracycline, chloramphenicol, oxytetracyline had to be present in barely biologically active amounts; (*b*) the effective drug (penicillin, streptomycin, bacitracin) had to be present in a bactericidal quantity, but not in great excess; (*c*) antagonism was most marked in experiments in which single doses of the drugs were administered in a definite time-relationship; the antagonizing agent first, the effective one later. Unless these conditions were fulfilled, antagonism occurred rarely in experimental animals and was of small magnitude (93 to 96). Consideration of the essential time-dose relationships indicates that antagonism could occur as the end result in clinical antibiotic therapy, only under very unusual circumstances. Thus, antagonism would not be expected to occur in the treatment of pneumococcal pneumonia with penicillin, 600,000 units daily, plus chlortetracycline, 1 gm. daily, since both drugs would be present in excess throughout the entire 24 hr. period (97). Moreover, antibiotic antagonism would be probable only in those diseases where recovery is dependent on the bactericidal effect of a chemotherapeutic agent, e.g., bacterial endocarditis, meningitis, osteomyelitis, and possibly pyelonephritis. In those circumstances the normal body defenses, particularly phagocytosis, are unable to effect cure. In respiratory tract disease, on the other hand, recovery, even without chemotherapy, can often be achieved by normal body defenses alone, and bactericidal effects of drugs are of little importance.

Of far greater clinical importance than antagonism, is the possible synergistic effect of antimicrobial agents. Jawetz & Gunnison (92) list the following forms of useful positive summation of drug action:

(*a*) In infections attributable to mixed bacterial populations (e.g., peritonitis following ruptured viscus) each member of a drug pair affects one portion of the bacterial flora.

(*b*) In certain infections one drug prevents the rapid emergence of variants resistant to the other drug (e.g., in tuberculosis, streptomycin resistance is delayed by simultaneous use of para-aminosalicyclic acid. Thus, the use of a drug combination permits much longer effective treatment (98).

(*c*) In some infections, one drug may strongly inhibit the microorganisms but may fail to kill them. Adding a second drug, which alone need

not have a manifest effect in the concentration employed, results in the rapid death of all exposed bacteria, and cure of the disease. The most thoroughly studied example in this category is bacterial endocarditis, where only bactericidal drugs or combinations are curative (99, 100, 101).

Can some drug pairs be designated as "good," resulting uniformly in synergism? Jawetz, *et al.* (102) studied this question in the laboratory and found that no pair of antibiotics was uniformly synergistic when tested against a variety of microorganisms. In every instance, the ultimate effect of the drug combination was found to depend on the behavior of the specific bacterial strain. These investigators were able, however, to formulate a tentative scheme of combined drug action (103). This scheme has been found practical by both Rantz (104) and Dowling (105) in the planning of laboratory experiments and the treatment of patients. A difficulty in the use of antibiotic combinations is the lack of a simple laboratory test. Present tests of sensitivity to antibiotic combinations are too complex for use in the ordinary clinical laboratory. The simpler procedures, such as the "disk" test, as pointed out by Peyre & Velu (106), are of little worth. To be of value, laboratory tests must measure the killing power of antibiotic combinations, as well as their bacteriostatic ability. Rantz (104), Chabbert (107), and others have developed simplified methods, but even these techniques are beyond the scope of the average laboratory. Combined antibiotic therapy will continue to be based on guesswork until more suitable laboratory tests are devised.

The effectiveness of combined antimicrobial therapy is well illustrated in the case of brucellosis. The action of a sulfonamide, streptomycin, chlortetracycline, oxytetracycline, or chloramphenicol, will strongly inhibit most strains of *Brucellae*. Yet not one of these drugs alone will completely destroy the organisms, partly because of lack of bactericidal effect, partly because the habitat of the organisms within cells protects them from drug action (108). Shaffer, *et al.* (109) proved that the combined action of streptomycin and any one of the drugs listed above, was capable of completely eradicating *Brucella* infection in experimental animals. Combinations of streptomycin and either chlortetracycline or oxytetracycline have been found equally effective in brucellosis in man (110, 111).

SULFONAMIDES

Although antibiotics were expected to replace sulfonamides, the production and consumption of sulfonamides increases every year (1). Triple sulfonamide mixtures which are relatively more soluble than single sulfonamides in the same total dose, were introduced several years ago. Schweinburg & Rutenburg (112), and Weinstein & Murphy (113) showed that the antibacterial activity of various mixtures was unpredictable, and suggested that "combinations of sulfonamides may have little clinical usefulness in

many instances since they are often not as effective as the single agents which compose them" (113). Lehr (114) considered the comparative merits of sulfisoxazole (Gantrisin) and a triple sulfonamide mixture. The triple sulfonamide was preferable for systemic drug levels, sulfisoxazole for high urinary levels. In pyelonephritis, as Birchall (115) pointed out, high levels of an antimicrobial drug in the urine have no effect on the focus of infection in the interstitial tissue of the kidney, but act merely as "urinary antiseptics." Thus sulfisoxazole would appear to be of little benefit in the treatment of upper urinary tract infection.

Eyles & Coleman (116) demonstrated a synergistic effect, in excess of simple additive action, between sulfadiazine and Daraprim, a pyrimidine derivative, in experimental toxoplasmosis. This is one of the very few acceptable instances of true synergism between sulfonamides and other antimicrobial substances. Such synergism has been claimed for combinations of penicillin and sulfonamides, but evidence has remained unconvincing. In the treatment of pneumococcal meningitis large doses of penicillin are apparently just as effective as combinations of penicillin with sulfonamide (117). In meningitis resulting from *Hemophilus influenzae* chlortetracycline used alone in large doses is as effective as mixtures of chlortetracycline, streptomycin, and sulfisoxazole (118). Even in meningococcal meningitis where intensive sulfonamide therapy was the choice until recently, large doses of penicillin (one million units intramuscularly every two hours) have given equally good results (119).

CHEMOTHERAPY OF TUBERCULOSIS

For some years streptomycin has been the mainstay of antimicrobial chemotherapy in tuberculosis. One of its important disadvantages is the rapid emergence of resistant microbial variants. In Blattberg & Ehrhorn's (120) experience about half the patients treated with one gram streptomycin daily for four months could be expected to carry resistant tubercle bacilli. Para-aminosalicyclic acid (PAS), by itself only a weak tuberculostatic agent, has remarkable ability in delaying the appearance of streptomycin-resistant tubercle bacilli, if both drugs are administered simultaneously (120, 121). Other drugs, like oxytetracycline, possess the same quality to a lesser degree (122).

Combined treatment with streptomycin and PAS was successful in suppressing a variety of tuberculous processes. One of its main disadvantages was the anorexia, and consequent failure to gain weight, induced by the large doses (20 gm. daily) of PAS necessary. Into this hopeful, though far from ideal, therapeutic picture, a bombshell burst in January 1952. In a fashion characteristic of our "newshappy" times, the story was first presented in newspapers and popular magazines: a new drug had been discovered which cured tuberculosis rapidly and painlessly. You simply ate a few pills every day and soon you were well. Photographs were shown of patients, dancing with joy on the wards, presumably after having been bedfast for

many months. Seriously ill consumptives everywhere prepared to leave
hospitals, believing that they could rapidly be cured at home. The public
press had a heyday describing the miracles that were about to happen. The
Executive Committee of the American Trudeau Society found it necessary
to issue a statement urging a more conservative attitude toward an essen-
tially unknown drug (123).

The powerful action of this drug, isonicotinic acid hydrazide (isoniazid)
against the tubercle bacillus was first described by workers at Sea View
Hospital in New York (124, 125). In the test tube, in experimental animals,
and in man, the new chemical was highly active against *Mycobacterium tuber-
culosis*, although affecting other microorganisms very little. Isoniazid was
readily absorbed from the intestinal tract, distributed through all body
fluids and tissues, and present in high concentrations in the spinal fluid (126).
In daily doses of 3 to 6 mg./kg., it produced no significant toxic reactions.

In a chronic disease like tuberculosis, where tissue reactions interfere
with the penetration of the drug to the microorganisms, long term drug
therapy is essential, and the development of microbial resistance becomes of
paramount importance. Most populations of tubercle bacilli contained a few
organisms resistant to high concentrations of isoniazid (127, 128, 129). In
laboratory experiments highly drug-resistant variants were readily obtained.
However, some of these resistant tubercle bacilli had greatly reduced patho-
genicity for laboratory animals (130).

The rapid emergence of isonazid-resistance like the problem of strepto-
mycin-resistance made it urgent that drug combinations be tried clinically.
In small, short-term studies, combined therapy with streptomycin and iso-
niazid was superior to treatment with isoniazid alone (131, 132). For the
first 2 to 3 months of treatment patients treated with isoniazid alone did as
well as those receiving combined drugs. Later, however, the combination
proved its superiority. In four months the majority of the sputa of patients
on isoniazid alone contained resistant tubercle bacilli, whereas with the
combination of isoniazid plus streptomycin, this emergence of resistance was
appreciably delayed (133).

To establish a firm foundation for the rational use of this valuable new
adjunct in therapy, large scale planned trials were begun in the United
States, by the U. S. Public Health Service, and in Great Britain, by the
Medical Research Council. In 649 patients in the American series, improve-
ment in pulmonary tuberculosis measured by clinical appearance, x-ray and
laboratory findings, continued up to 28 weeks of therapy, to about an equal
extent in groups given either isoniazid alone, streptomycin with isoniazid, or
streptomycin with PAS (134, 135). At about 28 weeks of treatment, tubercle
bacilli could be cultured from $\frac{1}{2}$ of the patients on isoniazid alone, but only
from $\frac{1}{3}$ of those on isoniazid with streptomycin. While the latter regimen
offered the greatest likelihood of "negative" sputum, it also afforded great
probability that the bacilli would have become resistant to both isoniazid
and streptomycin if the sputum had not become free of tubercle bacilli.

The other two regimens offered less chance of sputum conversion, but produced bacilli resistant to only one drug, leaving either streptomycin or isoniazid for subsequent use.

The Trials Committee of the British Medical Research Council expressed somewhat different opinions (136). Among 364 patients who had been treated for at least three months, the group receiving streptomycin 1 gm. daily plus isoniazid 200 mg. daily, had done slightly better in all respects than those receiving isonazid alone, or streptomycin plus PAS. At three months 62 per cent of culture-positive patients on isoniazid alone had resistant bacilli, compared to only 13 per cent of patients on the isoniazid-streptomycin combination. The latter combination was as effective as the streptomycin-PAS combination in delaying emergence of streptomycin-resistant bacilli. These bacteriological findings, of course, applied only to patients not harboring streptomycin-resistant bacilli from the beginning. In the latter, the inclusion of streptomycin in any combination had no effect whatsoever, and did not delay development of isoniazid resistance. The conclusions of the British group are significant: (a) None of the three drugs, isoniazid, streptomycin, or PAS, should be used by itself in the treatment of pulmonary tuberculosis, nor should any new drug be used by itself, except in controlled clinical trials. (b) To give a combination of these drugs to a patient whose organisms are already resistant to one of the two, appears to be tantamount to giving the other alone, and so is equally undesirable. It is therefore essential to test the new drug sensitivity of a patient's organisms before a course of chemotherapy is started. (c) A careful scrutiny of the history of previous chemotherapy may warn the clinician of possibly unsuitable combinations. At the present state of knowledge these appear to be very sound recommendations.

In patients with tuberculosis whose tubercle bacilli are resistant to the principal drugs, viomycin may be employed when chemotherapy is essential. This drug has good antituberculous activity (137) but because its toxicity appears to be much greater than that of other agents (138), it probably should be considered as "last resort" chemotherapy.

Tuberculous meningitis remains a formidable threat and challenge. In spite of a few innovations in therapeutic management the rate of relapses, deaths, or disabling neurological sequelae remains high (139). Success in treatment appears to depend on: (a) early institution of treatment; (b) maintenance of high levels of effective drugs in the central nervous system for many months; and (c) reduction of the arachnoiditis. Yet early diagnosis is often difficult. To maintain high levels of streptomycin within the meninges, intrathecal, as well as intramuscular, injections must be continued for many months, with the risk of irritation, reactions, toxicity, and drug resistance. Arachnoiditis and spinal block may prevent intrathecal drug administration and produce irreversible fibrous scarring and brain destruction (140). Recent developments offer hope for improved therapeutic results. Schedules combining isoniazid (5 to 10 mg./kg. daily by mouth) with twice weekly injections of streptomycin (1 to 2 gm.) result in high levels of drug in the nervous sys-

tem, yet minimize toxic side effects and the emergence of resistant tubercle bacilli. Such schedules can be maintained with ease for months, perhaps years, until definitive recovery is insured. Intrathecal administration of tuberculin, proposed earlier as a method for resolving the organizing fibrin of arachnoiditis (141) causes severe reactions. The same is true for the present streptokinase-streptodornase preparations (41); however, it seems probable that more satisfactory purified forms of fibrinolytic enzymes will be prepared in the future.

The intracellular multiplication of tubercle bacilli has been studied in tissue culture by Suter (142) and Mackaness (143). Various drugs differ greatly in their ability to penetrate the cell and reach intracellular organisms. Streptomycin diffuses into the cell very poorly, whereas both oxytetracycline and isoniazid reach similar concentrations inside cells and in extracellular fluid. Mackaness & Smith (144) demonstrated that streptomycin and isoniazid are probably synergistic against intracellular as well as extracellular tubercle bacilli. Oxytetracycline and isoniazid seem to be antagonistic. Hobby *et al.* (145) found both additive and apparent antagonistic effects between isoniazid and streptomycin, depending on the proportions of the drugs, in tuberculous infection of mice. Spain (146) pointed out that isoniazid commonly inhibits any inflammatory response and proposed that this nonspecific effect "may be one of the factors responsible for the rather sudden drop in temperature, marked diminution in sputum and increase in the feeling of well-being in isoniazid treated patients with tuberculosis."

Dubos (147) summarized with great wisdom the discordant aspects of chemotherapy of tuberculosis. Antimicrobial drugs might fail to kill tubercle bacilli in lesions, because of poor penetration of the drug, because of intracellular residence of bacilli, or because of tissue breakdown products which interfere with drug action. Even test tube cultures are often not "sterilized" by drugs: a few organisms may persist, perhaps because alterations in metabolism make them insusceptible to drug action. On the other hand, tuberculous lesions can sterilize themselves, perhaps through the action of various amines like spermine, organic acids, lysozyme, and various basic polypeptides of tissue, all of which affect tubercle bacilli. It is the complex interaction between drug, parasite and host, which determines the ultimate outcome.

ANTIBIOTICS OF SPECIAL USEFULNESS AND RESTRICTED APPLICATION

Bacitracin, neomycin, and polymyxin B which have been available for some years, have not been widely used because of their undesirable side effects. Although they can be administered with safety if proper knowledge and precautions are employed, these drugs have been shunned by physicians who feared their potential toxicity, but had no hesitation whatever in misusing the "safe" antibiotics with abandon. Now that the "safe" drugs have been found either less useful or not so "safe," the merits and limitations of bacitracin, neomycin, and polymyxin B deserve renewed scrutiny.

All three agents are poorly absorbed from mucous membranes, from skin,

and from the intestinal tract. They have strong bactericidal action on susceptible microorganisms on direct contact, but are much less effective in widespread tissue infection. They are therefore well suited to all forms of topical application (skin infection, wounds, intestinal tract). They do not readily induce hypersensitivity.

Bacitracin is chiefly useful in infections caused by gram-positive cocci which are resistant to other agents, and in combined antibiotic therapy (148, 149, 150). Although daily injections of from 40,000 to 80,000 units regularly give rise to proteinuria, slight hematuria and cylindruria, these manifestations of renal "irritation" tend to subside when treatment is discontinued.

Neomycin can also produce renal injury but its chief disadvantage is the insidious, and often late, damage to the auditory portion of the eighth nerve. Perhaps its greatest usefulness is the ability to suppress infection caused by *Proteus*, whether systemic or limited to the urinary tract, or wounds (151 to 153).

Among the polymyxins, polymyxin B and E are probably equally suited for clinical use (154). These polypeptides are exceedingly effective against many gram-negative bacilli, provided the infection is within a "closed system," such as the meninges or the urinary tract, and does not diffusely involve parenchymatous organs. Polymyxin B is at present the drug of choice in *Pseudomonas* infections, which are resistant to other drugs (155, 156). The widely expressed fear of nephrotoxicity of polymyxin B does not appear justified, except in patients with impaired kidney function. The drug appears safe, even when used for two weeks at dosage levels of 2.0 mg./kg./ day, provided initial kidney function is good (157).

Welch *et al.* (158) first proposed the use of mixtures of poorly absorbed antibiotics for suppression of the intestinal flora. Combinations of bacitracin, neomycin, and polymyxin B, or any two of these, have several advantages over the readily absorbed broad-spectrum antibiotics. They produce no gastrointestinal irritation, they are not absorbed significantly, and thus cannot give rise to sensitization. Since they remain in the intestinal tract, they cannot alter the normal flora of other parts of the body, e.g., the respiratory tract. Mixtures of these drugs suppressed the intestinal flora in less than 48 hr., much faster than the non-absorbable sulfonamides. Thus, were it not for the considerable cost, such mixtures have much to recommend them for pre-operative cleansing of the intestine (159).

Chemotherapy of fungus infections.—Advances in the treatment of deep mycoses have been slow. *Actinomycosis* frequently responded to prolonged administration of sulfonamides or penicillin, but not all strains of *Actinomyces bovis*, or *Nocardia asteroides* were susceptible to these agents. Oxytetracycline appears to be of use as alternative therapy (160).

Blastomycosis presented the first striking success in controlling a progressive deep mycosis. Whereas all antibiotics had been tried and had failed, the antimony preparation stilbamidine, in daily doses of 100 to 200 mg. given intravenously, resulted in striking suppression of lesions and symp-

toms, and apparent return of patients to normal. Stilbamidine is quite toxic, but careful management may avoid the more serious side effects and control the fungus infection [Schoenbach, *et al.* (161), Fink, *et al.* (162), Pariser, *et al.* (163)].

Other systemic fungus diseases have not yielded so satisfactorily. Prodigiosin has been advocated for disseminated coccidiodomycosis (164). Impressive improvement reported in a few patients has not been confirmed. The effectiveness of ethyl vanillate in disseminated histoplasmosis, likewise appears to be of small magnitude (165). In cryptococcus meningitis (torulosis) the antibiotic agent actidione has resulted in prolonged remissions, and perhaps cures, in a number of patients if sufficiently high doses were administered over a long period [Wilson & Duryea (166), Carton (167)]. Evaluation of chemotherapeutic results in this illness is made difficult by the notoriously slow course and the many spontaneous remissions and relapses [Beeson (168)].

THE ROLE OF HOST DEFENSES IN ANTIMICROBIAL THERAPY

Thomas recently reviewed the extensive literature dealing with the effects of cortisone on infection (169). The great majority of experimental viral, bacterial, and other infections appear to be significantly enhanced. Many statements have warned against spreading inapparent tuberculosis in man by cortisone administration. Almost every clinic has observed a patients who developed fulminating infection during cortisone administration, which could not be controlled by massive antimicrobial therapy. On the other hand, cortisone has been praised as a useful adjunct in the therapy of typhoid fever and Rocky Mountain spotted fever [Smadel *et al.* (170), Workman *et al.* (171)], and perhaps human brucellosis [Spink & Hall (172)].

The "enhancing" properties of cortisone on most invasive infectious processes can readily be explained by the pathological observations of Moon & Tershakovec (173) and Ebert & Barclay (174). Cortisone maintains vascular tone, reduces endothelial damage and permeability of capillaries, decreases diapedesis of leucocytes, and consequently reduces the inflammatory exudate. All these processes are useful in localizing and combating the infection, and the "increase in resistance of the capillary wall" induced by corticoid hormones diminishes effective host defenses.

While cortisone does not protect against bacterial exotoxins, it affords protection against endotoxins from gram-negative bacteria (175). Thus, it could be a valuable adjunct to the antibiotics which inhibit, or kill, the gram-negative organisms of typhoid, and brucellosis. The nonspecific antipyretic and analgesic effect of cortisone, used as a "super-aspirin" might possibly contribute to better resistance of the patient (176). Thus, in a limited number of infections, the beneficial "anti-endotoxic" effects of cortisone might balance its potentially harmful influence on bacterial dissemination.

Jawetz (177) observed eight years ago that in streptococcal infections of mice, penicillin reduced the bacterial population to a very low level, but that the normal host defenses eliminated the last few organisms. Eagle (178) later

described how the antibiotic injured the infecting microorganisms so that, for a time, they were unable to multiply, and how during this period they could be eliminated by host mechanisms. While the action of antibiotics in high concentration is often rapidly bactericidal, the ability of the host to recover completely from an infection may depend on the functioning of various cellular and humoral host mechanisms (179). In leucopenic animals, antibiotics are less effective in decimating the infecting microorganisms, than in normal animals (180). There have been occasional clinical observations of patients in whom an antibiotic failed to control an infection during treatment with cortisone, and success of the same antibiotic in the same dose when cortisone was withdrawn. Jawetz (181) studied the relationship of cortisone and antibiotics in experimental infections in animals. Using cortisone at human dosage levels (10 mg./kg./day), it was demonstrated that amounts of antibiotic failed to effect recovery which, in the absence of cortisone, resulted in rapid cure. Thus minimal curative doses of antibiotic probably eliminate bacteria with the aid of normal defense mechanisms of the host. Depression of these mechanisms by cortisone resulted in over-all therapeutic failure. With large excess of antibiotic, on the other hand, such effects were not demonstrable. Since clinical dosage of antibiotics is usually vastly in excess of the minimum curative dose, this cortisone effect is likely to influence therapy in only few patients.

RHEUMATIC FEVER AND GLOMERULONEPHRITIS

The relationship between infection with group A beta hemolytic streptococci and the development of rheumatic fever, appears well established. Prompt and adequate treatment of a streptococcal respiratory infection prevents rheumatic fever. Prevention of re-infection with hemolytic streptococci by chemoprophylaxis with sulfonamides or penicillin prevents recurrences of activity in rheumatic individuals (182). Infection with any streptococcal type is followed by type specific immunity and repeated infections with several different types appear to be a prerequisite for the development of the rheumatic state. In glomerulonephritis also, the temporal relationship with an antecedent beta hemolytic streptococcus infection is well established. Rammelkamp & Weaver (183) were struck by the great irregularity with which glomerulonephritis followed streptococcal respiratory infection. From a survey of all available evidence they discovered that glomerulonephritis followed almost exclusively infections by streptococcal types 12 and 4. These types appear to be "nephritogenic." Type specific immunity engendered by the initial streptococcal infection with type 12 or 4, would tend to protect the individual against re-infection with those same types. This is in accordance with the observation that repeated streptococcal infections play no part in re-activating glomerulonephritis. These epidemiological observations may be of material aid in understanding the pathogenesis of these disorders.

POLIOMYELITIS

Striking advances have been made toward better understanding and management of poliomyelitis, and perhaps toward the prevention of the

paralytic disease. Although poliomyelitis virus is a strongly neurotropic agent, it occurs in the throat, the intestinal tract and the blood stream of children with "minor" illness or asymptomatic infection (184).

The great majority of individuals acquire infection with poliomyelitis virus without developing any clinical symptoms or signs of paralytic involvement. Although many factors which convert subclinical, or non-paralytic, to paralytic disease remain unknown, various forms of stress have been clearly implicated. Tonsillectomy (185) and perhaps other types of operations on the upper respiratory tract are contraindicated during epidemic season. Strenuous physical activity can probably precipitate paralysis (186) and the rigors of prolonged, strenuous transportation may have equally adverse effects on the patient (187). In young women, pregnancy results in a higher incidence of paralysis. The injection of material into a limb predisposes to paralysis of that limb (188).

A variety of improvements in clinical management of the paralytic stage have been devised and the relative indications for the use of tracheotomy, oxygen therapy, respirators, are being defined. Perhaps the most dramatic results of various improvised treatment methods were seen during a huge outbreak of poliomyelitis in Copenhagen in 1952. In a period of four months, a single hospital was called upon to care for 866 cases with paralysis. During the peak of the epidemic, as many as 50 paralytic cases were admitted daily. While the previous mortality of patients with respiratory paralysis was almost 80 per cent, the ingenious use of tracheotomy, combined with frequent aspiration and manual bag ventilation, reduced the mortality among 316 such patients to 40 per cent [Lassen (189)].

Experiments in monkeys some years ago indicated that human gamma globulin administered before, or soon after, an infectious dose of virus, gave passive protection against paralysis. The results of large scale human experiments were summarized by Hammon and his group (190). In three epidemic areas gamma globulin was given intramuscularly in a dose of 0.14 cc. per pound body weight, to half of 55,000 children; the other half received a similar injection of gelatin. Between 2 and 13 weeks after the injections, 76 paralytic cases occurred, only 19 were in the gamma globulin group, 57 in the control group. It has been calculated that in severe epidemics, from 300 to 2000 injections would be necessary to prevent one paralytic case. It is estimated that 10 per cent of secondary cases in a family will occur 7 days, or later, from the diagnosis of the "index case." These secondary cases might be modified or prevented by prompt injection of gamma globulin.

Because of the obvious limitations in available gamma globulin, and because of the short passive protection (not over 8 weeks) following an injection, a large proportion of all available gamma globulin collected by the Red Cross will be administered to household contacts of diagnosed cases of poliomyelitis. The pressure on the physician to administer such injections will be great. The benefits of the entire, very costly program appear quite dubious. In many families, undoubtedly, simultaneous exposure of several members

occurs from a common source (191). The virus spreads rapidly through the family, and by the time the "index case" is diagnosed, the infection is usually established and the ultimate fate largely determined for each family member. It seems doubtful that gamma globulin will influence developments under such circumstances.

In contrast to this impractical, short-lived "prophylaxis" with gamma globulin, the development of techniques which may lead to active immunization against poliomyelitis, gives rise to great hopes. Three separate approaches to the production of an immunizing vaccine deserve mention.

The first is based on the tissue culture techniques developed by Enders and his group (192, 193). These methods permit the growth in test tubes of all three types of poliomyelitis virus, with the potential production of large amounts of virus. Neutralization of the virus by specific antibodies can be detected by observing the "cytopathogenic effect" *in vitro*. This improved method for serological studies is applicable to surveys, and to detect individual susceptibility to any given type of poliomyelitis virus. Salk (194) found that roller-tube grown virus, killed with formalin, and administered intramuscularly with an adjuvant to human volunteers, gave rise to high antibody titers. While these studies give only preliminary information concerning the antigenic stimulus of such viral preparations, and in no way indicate that a practical vaccine is at hand, they point the way to future investigations.

A second development of great potential significance lies in the adaptation of human poliomyelitis viruses to other animals. The resultant strains lose pathogenicity for the human host, but retain their immunizing ability. This has been accomplished for type 2 poliomyelitis viruses, which were adapted to the chick embryo (195, 196). If other viral types can likewise be grown in fertile eggs, mass production will be possible and economical, and such virus material could be employed in a vaccine. Again, no immediate practical application is evident at this time, but the potentialities are great.

The third interesting development centers around the work of Koprowski (197), who discovered a strain of type 2 poliomyelitis virus which was nonpathogenic when given orally to monkeys and humans, but resulted in the formation of antibodies. In experimental animals a certain amount of crossimmunity with other virus types was also observed. This approach emphasizes the use of nonpathogenic live "virus-vaccine" administered by a "natural" route, and resulting in an asymptomatic infection. The successful immunization with vaccines of smallpox and yellow fever, which are based on the same principle, indicates that this work deserves much attention.

ETIOLOGIC STUDIES ON OTHER DISEASES

Exanthem subitum, the long familiar rose rash of infants, was shown by transmission studies, to be attributable to a virus [Kempe (198)]. The virus can probably be carried by adults who may serve as source of infection for small children.

A "new disease" manifested by a febrile lymphadenitis progressing to the suppuration of lymph nodes, has been encountered in several parts of the world, and called "cat scratch fever" (199, 200, 201). The illness has been transmitted to monkeys by inoculation of pus from a lymph node. Elementary bodies, suggesting a large virus, were seen in smears (200). Heat-inactivated pus injected intradermally produced a positive skin reaction, resembling that of a Frei test. The actual role of cats in this entity is questionable.

Further doubt as to the specific nature of suppurating lymphadenopathy was raised by the finding that toxoplasmosis may closely simulate "cat scratch fever." Siim (202) described a vague, febrile illness in children with lymphadenopathy and occasional respiratory symptoms, which was diagnosed acquired toxoplasmosis by serological test. Feldman (203) pointed out that the manifestations of acquired toxoplasmosis may be protean, including fever, rashes, encephalitis, myalgia and arthralgia, lymphadenopathy, and pneumonitis. The clinical picture may resemble infectious mononucleosis, but the heterophile agglutination test remains negative. Acquired toxoplasmosis in the adult was diagnosed by Kass et al. (204) and Sexton, et al. (205), with isolation of organisms in the tissues at autopsy, and typical serological findings. In a similar patient who recovered, toxoplasma organisms were recovered from an excised suppurating lymph gland by Armstrong & MacMurray (206). Thus, toxoplasma infection may account for some of the cases labeled "cat scratch fever." A further indication of the prevalence of toxoplasma infection in adults was the morphological identification of toxoplasma-like organisms in 41 eyes enucleated because of chronic chorioretinitis (207).

The Korean War has brought to light another "new" disease of infectious nature, which is also thought to be of viral origin. Hemorrhagic fever has been contracted by several hundred soldiers in limited sections of the front, apparently through the bite of arthropods. The disease results in vascular insults, which produce striking patho-physiological derangements, particularly of renal function (208, 209).

CONCLUSIONS

Lord Horder has recently stated that " . . . although many epidemic diseases of previous centuries have disappeared the automobile has almost replaced the microbe as a menace . . . " (210). The present review attempts to point out that the vast developments in antimicrobial therapy serve as powerful tools for the physician in his attempts to control infection, but have not removed "the microbe as a menace." The Hunterian Society in London debated, on November 17, 1952, the proposition "that the continued advance in medicine will produce more problems than it solves." After several somewhat facetious speeches the proposition carried by 59 votes to 47 (211). The adjustment of the microbial world to the impact of chemotherapy serves as an illustration that the majority opinion may be correct.

LITERATURE CITED

1. Welch, H., *Antibiotics & Chemotherapy*, 2, 279–80 (1952)
2. Finland, M., and Weinstein, L., *New Engl. J. Med.*, 248, 220–26 (1953)
3. Jawetz, E., *Arch. Internal Med.*, 90, 301–9 (1952)
4. Waldbott, G. L., *J. Am. Med. Assoc.*, 139, 526–27 (1949)
5. Berne, R. M., *New Engl. J. Med.*, 242, 814–17 (1950)
6. Everett, R., *J. Am. Med. Assoc.*, 146, 1314–15 (1951)
7. Thomson, W. O., *Brit. Med. J.*, II, 70–72 (1952)
8. Higgins, G. A., and Rothchild, T. P. E., *New Engl. J. Med.*, 247, 644–46 (1952)
9. Mayer, P. S., Mosko, M. M., Schutz, P. J., Osterman, F. A., Steen, L. H., and Baker, L. A., *J. Am. Med. Assoc.*, 151, 351–53 (1953)
10. Feinberg, S. M., Feinberg, A. R., and Moran, C. F., *J. Am. Med. Assoc.*, 152, 114–18 (1953)
11. Marsh, R. R., and Tillotson, I. G., *New Engl. J. Med.*, 245, 17–20 (1951)
12. Reichlin, S., Loveless, M. H., and Kane, E. G., *Ann. Internal Med.*, 91, 113–19 (1953)
13. Adelson, L., *J. Pediat.*, 39, 346–53 (1951)
14. Spring, M., *J. Am. Med. Assoc.*, 147, 1139–41 (1951)
15. Butterly, J. M., and Fishman, L., *J. Am. Med. Assoc.*, 148, 370–72 (1952)
16. Whipple, R. L., and Bloom, W. L., *J. Lab. Clin. Med.*, 36, 635–39 (1950)
17. Gittell, G., *J. Am. Med. Assoc.*, 147, 1141 (1951)
18. Merliss, R. R., and Hoffman, A., *New Engl. J. Med.*, 245, 328–30 (1951)
19. Pepinsky, R., and Watanabe, T., *Science*, 115, 541 (1952)
20. Gyorgy, P., Stokes, J., Jr., Goldblatt, H., and Popper, H., *J. Exptl. Med.*, 93, 513–22 (1951)
21. Lepper, M. H., Wolfe, C. K., Zimmerman, H. J., Caldwell, E. R., Spies, H. W., and Dowling, H. F., *Arch. Internal Med.*, 88, 271–83 (1951)
22. Rutenburg, A. M., and Pinkes, S., *New Engl. J. Med.*, 247, 797–800 (1952)
23. Jacob, S., Schweinburg, F. B., and Rutenburg, A. M., *Proc. Soc. Exptl. Biol. Med.*, 78, 121–22 (1951)
24. Bateman, J. C., Barberio, J. R., Cromer, J. K., and Klobb, C. T., *Antibiotics & Chemotherapy*, 3, 1–15 (1953)
25. Bateman, J. C., Barberio, J. R., Grice, P., Klobb, C. T., and Pierpont, H., *Arch. Internal Med.*, 90, 763–73 (1952)
26. Carr, P. T., Brown, H. A., Hodgson, C. H., and Heilmbin, F. R., *J. Am. Med. Assoc.*, 143, 1223–25 (1950)
27. Welch, H., *J. Am. Med. Assoc.*, 152, 200 (1953)
28. McKay, R. J., Davies, J. A., Berenberg, W., and Lowd, H. M., *J. Am. Med Assoc.*, 147, 818–21 (1951)
29. Heck, W. E., and Hinshaw, H. C., *Veterans Administration, 12th Conference on Chemotherapy of Tuberculosis* (Atlanta, Ga., 1953)
30. Volini, I. F., Greenspan, I., Ehrlich, L., Gonner, J. A., Felsenfeld, O. F., and Schwartz, S. O., *J. Am. Med. Assoc.*, 143, 1333–35 (1950)
31. Editorial, *J. Am. Med. Assoc.*, 149, 840 (1952)
32. Editorial, *New Engl. J. Med.*, 247, 183–85 (1952)
33. Lewis, C. N., Putnam, L. E., Hendricks, F. D., Kerlan, I., and Welch, H., *Antibiotics & Chemotherapy*, 2, 601–9 (1952)
34. Weinstein, L., *Am. J. Med. Sci.*, 214, 56–63 (1947)
35. Appelbaum, E., and Leff, W. A., *J. Am. Med. Assoc.*, 138, 119–21 (1948)

36. Yow, E. M., *J. Am. Med. Assoc.*, **149**, 1184–88 (1952)
37. Waisbren, B. A., *Arch. Internal Med.*, **88**, 467–88 (1951)
38. Jawetz, E., *Arch. Internal Med.*, **89**, 90–98 (1952)
39. Editorial, *Lancet*, **I**, 1310–11 (1951)
40. Jackson, D. M., Lowbury, E. J. L., and Topley, E., *Lancet*, **II**, 137–47 (1951)
41. Knight, V., Hardy, R. C., and Negrin, J., *J. Am. Med. Assoc.*, **149**, 1395–96 (1952)
42. Wheat, R. P., Zuckerman, A., and Rantz, L. A., *Arch. Internal Med.*, **88**, 461–67 (1952)
43. Janbon, M., Bertrand, L., Salvaing, J., and Labange, R., *Montpellier Medical*, **95**, 300–11 (1952)
44. Jackson, G. G., Haight, T. H., Kass, E. H., Womack, C. R., Gocke, T. M., and Finland, M., *Ann. Internal Med.*, **35**, 1175–1202 (1951)
45. Bernhart, G., *Schweiz. med. Wochschr.*, **82**, 1335–37 (1952)
46. Reiner, L., Schlesinger, M. J., and Miller, G. M., *Arch. Pathol.*, **54**, 39 (1952)
47. Dearing, W. H., and Heilman, F. R., *Proc. Staff Meetings Mayo Clinic*, **28**, 121–34 (1953)
48. McGovern, J. J., Parrott, R. H., Emmons, C. W., Ross, S., Burke, F. G., and Rice, E. C., *New Engl. J. Med.*, **248**, 397–403 (1953)
49. Bierman, H. A., and Jawetz, E., *J. Lab. Clin. Med.*, **37**, 394–401 (1951)
50. McVay, L. V., Jr., and Sprunt, D. H., *Proc. Soc. Exptl. Biol. Med.*, **78**, 759–61 (1951)
51. Kligman, A. M., *J. Am. Med. Assoc.*, **149**, 979–983 (1952)
52. Brown, C., Jr., Propp, S., Guest, C. M., Beebe, R. T., and Early, L., *J. Am. Med. Assoc.*, **152**, 206–7 (1953)
53. Moore, M., *J. Lab. Clin. Med.*, **37**, 703–12 (1951)
54. Huppert, M., MacPherson, D. A., and Cazin, J., *J. Bact.*, **65**, 171–76 (1953)
55. Seligman, E., *Proc. Soc. Exptl. Biol. Med.*, **79**, 481–83 (1952)
56. Brown, R., Hazen, E. L., and Mason, A., *Science*, **117**, 609–10 (1953)
57. Paine, T. F., Jr., *Antibiotics & Chemotherapy*, **2**, 653–57 (1952)
58. Mountain, D. C., and Krumenacher, F. P., *Am. J. Med. Sci.*, **225**, 274–80 (1953)
59. Boe, J., and Vogelsjg, T. M., *Acta Pathol. Microbiol. Scand.*, **29**, 368–72 (1951)
60. Needham, G. M., and Nichols, D. R., *J. Lab. Clin. Med.*, **41**, 150–56 (1953)
61. Clarke, S. K. R., Dalgleish, P. G., and Gillespie, W. A., *Lancet*, **I**, 1132–35 (1952)
62. Sherris, J. C., and Florey, M. E., *Lancet*, **I**, 309–12 (1951)
63. Finland, M., Haight, T. H., Wilcox, C., and Broderick, M. K., *Arch. Internal Med.*, **91**, 143–58 (1953)
64. Reiss, E., Pulaski, E. J., Amspacher, W. H., and Contreras, A. A., *New Engl. J. Med.*, **246**, 611–12 (1952)
65. Koch, M. L., and Bourgeois, R. W., *Antibiotics & Chemotherapy*, **2**, 229–233 (1952)
66. Prissick, F. H., *Am. J. Med. Sci.*, **225**, 299–319 (1953)
67. Monnier, J. J., and Schoenbach, E. B., *Antibiotics & Chemotherapy*, **1**, 472–86 (1951)
68. Kaipanen, W. J., *Ann. Med. Exptl. et Biol. Fenniae*, **30**, 61–71 (1952)
69. Gocke, T. M., and Finland, M., *J. Lab. Clin. Med.*, **38**, 719–35 (1951)
70. Herrell, W. E., Heilman, F. R., and Wellman, W. E., *Ann. N. Y. Acad. Sci.*, **53**, 448–58 (1950)
71. Finland, M., Wilcox, C., Wright, S. S., and Purcell, E. M., *Proc. Soc. Exptl. Biol. Med.*, **81**, 725–29 (1953)

72. Haight, T. H., Wilcox, C., and Finland, M., *J. Lab. Clin. Med.*, **39,** 637–48 (1952)
73. Welch, H., Randall, W. A., Putnam, L. E., and Hendricks, F. D., *Antibiotics & Chemotherapy*, **2,** 249–54 (1952)
74. Scheierson, S. S., *J. Lab. Clin. Med.*, **40,** 48–57 (1952)
75. McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M., and Smith, J. W., *Antibiotics & Chemotherapy*, **2,** 281–83 (1952)
76. Tanner, F. W., Jr., English, A. R., Lees, T. M., and Routien, J. B., *Antibiotics & Chemotherapy*, **2,** 441–43 (1952)
77. Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J., *Antibiotics & Chemotherapy*, **2,** 693–96 (1952)
78. Haight, T. H., and Finland, M., *Proc. Soc. Exptl. Biol. & Med.*, **81,** 175–93 (1952)
79. Purcell, E. M., Wright, S. S., and Finland, M., *Proc. Soc. Exptl. Biol. Med.*, **82,** 124–31 (1953)
80. Smith, J. W., Dyke, R. W., and Griffith, R. S., *J. Am. Med. Assoc.*, **151,** 805–10 (1953)
81. Kirby, W. M. M., Maple, F. M., and O'Leary, B., *Antibiotics & Chemotherapy*, **3,** 473–77 (1953)
82. Jensen, K. A., Dragsted, P. J., Kiaer, I., Nielsen, E. J., and Fredericksen, E., *Ugeskrift Laeger*, **113,** 1035–39 (1951)
83. Grigsby, M. E., Haight, T. H., and Finland, M., *New Engl. J. Med.*, **247,** 807–11 (1952)
84. Report of Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **151,** 1105 (1953)
85. Elias, W., Price, A. H., and Merrion, H. J., *Antibiotics & Chemotherapy*, **1,** 491–98 (1951)
86. Stollermann, G. H., and Rusoff, J. H., *J. Am. Med. Assoc.*, **150,** 1571–75 (1952)
87. Jawetz, E., *Arch. Internal Med.*, **90,** 301–9 (1952)
88. Bliss, E. A., Warth, P. T., and Long, P. H., *Bull. Johns Hopkins Hosp.*, **90,** 149–69 (1952)
89. Lepper, M. H., and Dowling, H. F., *Arch. Internal Med.*, **88,** 489–94 (1951)
90. Editorial, *J. Am. Med. Assoc.*, **147,** 513–14 (1951)
91. Jawetz, E., and Gunnison, J. B., *J. Am. Med. Assoc.*, **150,** 693–95 (1952)
92. Jawetz, E., and Gunnison, J. B., *Pharmacol. Reviews*, **5,** 175–92 (1953)
93. Ahern, J. J., Burnell, J. M., and Kirby, W. M. M., *Proc. Soc. Exptl. Biol. Med.*, **79,** 568–71 (1952)
94. Speck, R. S., and Jawetz, E., *Am. J. Med. Sci.*, **223,** 280–85 (1952)
95. Jackson, G. G., Lepper, M. H., *Am. J. Med. Sci.*, **225,** 525–34 (1953)
96. Lepper, M. H., Jackson, G. G., Dowling, H. F., and Seto, J., *Am. J. Med. Sci.*, **225,** 648–56 (1953)
97. Ahern, J. J., and Kirby, W. M. M., *Arch. Internal Med.*, **91,** 197–203 (1953)
98. Klein, M., and Schorr, S. E., *J. Bact.*, **65,** 454–65 (1953)
99. Hunter, T. H., *Bull. N. Y. Acad. Med.*, **28,** 213–28 (1952)
100. Garrod, L. P., *Brit. Med. J.*, **I,** 953–57 (1953)
101. Martin, R., Sureau, B., and Chabbert, Y., *Bull. soc. méd. Paris*, **68,** 1192–1201 (1952)
102. Jawetz, E., Gunnison, J. B., Bruff, J. A., and Coleman, V. R., *J. Bact.*, **64,** 29–39 (1952)
103. Jawetz, E., Gunnison, J. B., *Antibiotics & Chemotherapy*, **2,** 243–48 (1952)

104. Rantz, L. A., and Randall, E., *Antibiotics & Chemotherapy*, **2**, 645–52 (1952)
105. Dowling, H. F., Lepper, M. H., and Jackson, G. G., *J. Am. Med. Assoc.*, **151**, 813–15 (1953)
106. Peyre, M., and Velu, H., *Rev. immunol.*, **16**, 142–56 (1952)
107. Chabbert, Y., *Ann. inst. Pasteur*, **84**, 545–61 (1953)
108. Magoffin, R. L., and Spink, W. W., *J. Lab. Clin. Med.*, **37**, 924–30 (1951)
109. Shaffer, J. M., Kucera, C. J., and Spink, W. W., *J. Immunol.*, **70**, 31–38 (1953)
110. Herrell, W. E., and Barber, T. E., *J. Am. Med. Assoc.*, **144**, 519–24 (1950)
111. Magill, G. B., and Killough, J. H., *Arch. Internal Med.*, **91**, 204–11 (1953)
112. Schweinburg, F. B., and Rutenburg, A. M., *Proc. Soc. Exptl. Biol. Med.*, **74**, 480–85 (1950)
113. Weinstein, L., and Murphy, E. B., *Proc. Soc. Exptl. Biol. & Med.*, **80**, 519–22 (1952)
114. Lehr, D., *Antibiotics & Chemotherapy*, **3**, 71–93 (1953)
115. Birchall, R., *J. Urol.*, **68**, 798–803 (1952)
116. Eyles, D. E., and Coleman, N., *Antibiotics & Chemotherapy*, **3**, 483–90 (1953)
117. Alexander, J. D., Flippin, H. F., and Eisenberg, G. M., *Arch. Internal Med.*, **91**, 440–47 (1953)
118. Lepper, M. H., Wehrle, P. F., and Blatt, N., *Am. J. Diseases Children*, **83**, 763–68 (1952)
119. Lepper, M. H., Dowling, H. F., Wehrle, P. F., Blatt, N. H., Spies, H. W., and Brown, M., *J. Lab. Clin. Med.*, **40**, 891–900 (1952)
120. Blattberg, B., and Ehrhorn, H., *J. Lab. Clin. Med.*, **34**, 358–67 (1949)
121. Friedman, B., Sale, L., and Goldman, A., *Am. J. Med. Sci.*, **224**, 53–56 (1952)
122. Miller, F. L., Sands, J. H., Walker, R., Dye, W. E., and Tempel, C. W., *Am. Rev. Tuberc.*, **66**, 534–41 (1952)
123. Executive Committee, American Trudeau Society, *Am. Rev. Tuberc.*, **65**, 649–52 (1952)
124. Grunberg, E., and Schnitzer, R. J., *Bull. Sea View Hospital*, **13**, 3–11 (1952)
125. Robitzek, E. H., Selikoff, I. J., and Ornstein, G. C., *Bull. Sea View Hospital*, **13**, 27–51 (1952)
126. Elmendorf, D. F., Cawthon, W. U., Muschenheim, C., and McDermott, W., *Am. Rev. Tuberc.*, **65**, 429–42 (1952)
127. Szybalski, W., and Bryson, V., *Am. Rev. Tuberc.*, **65**, 768–70 (1952)
128. Hobby, G. L., and Lenert, T. F., *Am. Rev. Tuberc.*, **65**, 771–74 (1952)
129. Knox, R., King, M. B., and Woodroffe, R. C., *Lancet*, **II**, 854–68 (1952)
130. Barry, V. C., Conalty, M. L., and Gaffney, E., *Lancet*, **I**, 978–79 (1953)
131. Joiner, C. L., MacLean, K. S., Pritchard, E. K., Anderson, K., King, M. B., Collard, P., and Knox, R., *Lancet*, **II**, 843–49 (1952)
132. Thoren, M., and Hinshaw, H. C., *Stanford Med. Bull.*, **10**, 316–18 (1952)
133. Dye, W. E., Lynch, H. P., Brees, A. G., *Am. Rev. Tuberc.*, **67**, 106–8 (1953)
134. Mount, F. W., and Ferebee, S. H., *Am. Rev. Tuberc.*, **67**, 539–43 (1953)
135. Cooperative Investigation, U. S. Public Health Service, *Am. Rev. Tuberc.*, **67**, 553–67 (1953)
136. Tuberculosis Chemotherapy Trials Committee, Medical Research Council, *Brit. Med. J.*, **I**, 521–37 (1953)
137. Hobby, G. L., Lenert, T. F., Donikian, M., and Pikula, D., *Am. Rev. Tuberc.*, **63**, 17–24 (1951)
138. Werner, C. A., Tompsett, R., Muschenheim, C., and McDermott, W., *Am. Rev. Tuberc.*, **63**, 49–61 (1951)
139. Smith, K. M., *Am. J. Med. Sci.*, **225**, 657–59 (1953)

140. Ravreby, L., Caron, G. H., and Vasilios, A. G., *New Engl. J. Med.*, **246**, 883–89 (1952)
141. Atkins, E. C., and Cummings, M. M., *New Engl. J. Med.*, **247**, 715–17 (1952)
142. Suter, E., *J. Exptl. Med.*, **96**, 137–50 (1952)
143. Mackaness, G. B., and Smith, N., *Am. Rev. Tuberc.*, **66**, 125–260 (1952)
144. Mackaness, G. B., and Smith, N., *Am. Rev. Tuberc.*, **67**, 322–40 (1953)
145. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D., *Am. Rev. Tuberc.*, **67**, 808–27 (1953)
146. Spain, D. M., *Proc. Soc. Exptl. Biol. Med.*, **82**, 358–60 (1953)
147. Dubos, R. J., *Am. Rev. Tuberc.*, **67**, 874–77 (1953)
148. Meleney, F. L., Longacre, A. B., Altemeier, W. A., Reisner, E., Pulaski, E. J., and Zintel, H. A., *Surg. Gynecol. Obstet.*, **89**, 657 (1949)
149. Charet, R., and Siegel, I., *Arch. Internal Med.*, **90**, 250–57 (1952)
150. Wallach, R., and Pomerantz, N., *Arch. Internal Med.*, **88**, 840–46 (1951)
151. Waisbren, B. A., and Spink, W. W., *Bull. Univ. Minn. Hosp.*, **21**, 530–51 (1950)
152. Duncan, G. G., Clancy, C. F., Wolgamot, J. R., and Beidleman, B., *J. Am. Med. Assoc.*, **145**, 75–79 (1951)
153. Livingood, C., *J. Am. Med. Assoc.*, **148**, 334–39 (1952)
154. Swift, P. N., and Bushby, S. R. M., *Lancet*, **I**, 110–12 (1953)
155. Jawetz, E., *Arch. Internal Med.*, **89**, 90–98 (1952)
156. Ragan, B. M., Krersky, D., Milger, A., and Locke, M., *J. Lab. Clin. Med.*, **37**, 402–14 (1951)
157. Hopper, J., Jawetz, E., and Hinman, F., *Am. J. Med. Sci.*, **225**, 402–9 (1953)
158. Welch, H., Randall, W. A., and Price, C. W., *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 487–89 (1950)
159. Jawetz, E., and Bierman, H. F., *Gastroenterology*, **21**, 130–47 (1952)
160. Lane, S. L., Kutscher, A. H., and Shaves, R., *J. Am. Med. Assoc.*, **151**, 986–88 (1953)
161. Schoenbach, E. B., Miller, J. M., Ginsberg, M., Long, P. H., *J. Am. Med. Assoc.*, **146**, 1317–18 (1951)
162. Fink, J. C., Vanderploeg, D. E., and Moursund, M. P., *J. Am. Med. Assoc.*, **151**, 1395–97 (1953)
163. Pariser, H., Levy, E. D., and Rawson, A. J., *J. Am. Med. Assoc.*, **152**, 129–31 (1953)
164. Wier, R. H., Egeberg, R. O., Lack, A. R., and Leiby, G. M., *Am. J. Med. Sci.*, **224**, 70–76 (1952)
165. Ellis, F. F., Scott, R. J., and Miller, J. M., *Antibiotics & Chemotherapy*, **2**, 347–50 (1952)
166. Wilson, H. M., and Duryea, A. W., *Arch. Neurol. Psychiat.*, **66**, 470 (1951)
167. Carton, C. A., *Ann. Internal Med.*, **37**, 123–45 (1952)
168. Beeson, P. B., *Arch. Internal Med.*, **89**, 797–801 (1952)
169. Thomas, L., *Ann. Rev. Med.*, **3**, 1–24 (1952)
170. Smadel, J. E., Ley, H. L., and Diercks, F. H., *Ann. Internal Med.*, **34**, 10 (1951)
171. Workman, J. B., Hightower, J. A., Borges, F. J., Furman, J. E., and Parker, R. T., *New Engl. J. Med.*, **246**, 962–66 (1952)
172. Spink, W. W., and Hall, W. H., *J. Clin. Invest.*, **31**, 958–68 (1952)
173. Moon, V. H., and Tershakovec, G. A., *Proc. Soc. Exptl. Biol. Med.*, **79**, 63–66 (1952)
174. Ebert, R. H., and Barclay, W. R., *Ann. Internal Med.*, **37**, 506–18 (1952)
175. Boyer, F., and Chedid, L., *Ann. inst. Pasteur*, **84**, 453–57 (1953)
176. Kass, E. H., and Finland, M., *New Engl. J. Med.*, **243**, 693–95 (1950)

177. Jawetz, E., *Arch. Internal Med.*, **77**, 1–15 (1946)
178. Eagle, H., Fleischman, R., and Musselman, A. D., *Ann. Internal Med.*, **33**, 544–71 (1950)
179. Eagle, H., Fleischman, R., and Levy, M., *Proc. Soc. Exptl. Biol. Med.*, **82**, 201–3 (1953)
180. Gowans, J. L., *Brit. J. Exptl. Pathol.*, **34**, 195–201 (1953)
181. Jawetz, E., *J. Clin. Invest.*, **32**, 578–79 (1953)
182. Statements of American Heart Association Council on Rheumatic Fever and Congenital Heart Disease, *J. Am. Med. Assoc.*, **151**, 141 (1953)
183. Rammelkamp, C. H., Jr., and Weaver, R. S., *J. Clin. Invest.*, **32**, 345–58 (1953)
184. Horstmann, D. M., and McCollum, R. W., *Proc. Soc. Exptl. Biol. Med.*, **82**, 434–37 (1953)
185. Francis, T., Jr., Krill, C. E., Toomey, J. A., and Mack, W. N., *J. Am. Med. Assoc.*, **119**, 1392–95 (1942)
186. Albrecht, R. M., and Locke, F. B., *J. Am. Med. Assoc.*, **146**, 769–71 (1951)
187. Brahdy, M. B., and Katz, S. H., *J. Am. Med. Assoc.*, **146**, 772–74 (1951)
188. Martin, J. K., *Arch. Disease Childhood*, **25**, 1–14 (1950)
189. Lassen, H. C. A., *Lancet*, **I**, 37 (1953)
190. Hammon, W. M., Coriell, L. L., Wehrle, P. F., and Stokes, J., Jr., *J. Am. Med. Assoc.*, **151**, 1272–85 (1953)
191. Fox, M. J., and Chamberlain, J., *J. Am. Med. Assoc.*, **151**, 1099–1101 (1953)
192. Enders, J. F., *J. Immunol.*, **69**, 639–44 (1952)
193. Robbins, F. C., Weller, T. H., and Enders, J. F., *J. Immunol.*, **69**, 673–94 (1952)
194. Salk, J. E., *J. Am. Med. Assoc.*, **151**, 1081–98 (1953)
195. Cabasso, V. J., Stevvins, M. R., Dutcher, R. M., and Cox, H. R., *Proc. Soc. Exptl. Biol. Med.*, **81**, 525–29 (1952)
196. Roca-Garcia, M., Moyer, A. W., and Cox, H. R., *Proc. Soc. Exptl. Biol. Med.*, **81**, 519–25 (1952)
197. Koprowski, H., Jervis, G. A., Norton, T. W., and Nelson, D. J., *Proc. Soc. Exptl. Biol. Med.*, **82**, 277–80 (1953)
198. Kempe, C. H., Shaw, E. B., Jackson, J. R., and Silver, H. K., *J. Pediat.*, **37**, 561–68 (1950)
199. Greer, W. E. R. and Keefer, C. S., *New Engl. J. Med.*, **244**, 545–48 (1951)
200. Mollaret, P., Reilly, J., Bastin, R., and Tournier, P., *Presse méd.*, **59**, 701–4 (1951)
201. Daniels, W. B., and MacMurray, F. G., *Ann. Internal Med.*, **37**, 697–713 (1952)
202. Siim, J. C., *J. Am. Med. Assoc.*, **147**, 1641–44 (1951)
203. Feldman, H. A., *Am. J. Trop. Med. Hyg.*, **2**, 420–28 (1953)
204. Kass, E. H., Andrus, S. B., Adams, R. D., Turner, F. C., and Feldman, H. A., *Arch. Internal Med.*, **89**, 759–82 (1952)
205. Sexton, R. C., Eyles, D. E., Dillman, R. E., *Am. J. Med.*, **14**, 366–77 (1953)
206. Armstrong, C., and MacMurray, F. G., *J. Am. Med. Assoc.*, **151**, 103–4 (1953)
207. Wilder, H. C., *Arch. Ophthalmol (Chicago)*, **47**, 425 (1952)
208. Katz, S., Leedham, C. L., and Kessler, W. H., *J. Am. Med. Assoc.*, **150**, 1363–66 (1952)
209. Barbero, G. J., Katz, S., Kraus, H., and Leedham, C. L., *Arch. Internal Med.*, **91**, 177–96 (1953)
210. Lord Horder, *New Engl. J. Med.*, **248**, 381 (1953)
211. Hunterian Society Debate, *Brit. Med. J.*, **2**, 1202 (1952)

DISEASES OF THE GASTROINTESTINAL TRACT[1]

By Franklin Hollander and Henry D. Janowitz

Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York, N. Y.

The following review is devoted to the discussion of selected topics on diseases of the digestive tract, rather than exhaustive treatment of individual papers. Whenever possible, an attempt has been made to discuss a disease in terms of disorders of physiology associated with it. However, because of the biases of the reviewers, the irregular appearance in the literature of papers in the diverse areas which ought to be covered by such a review, and especially the limited space available, many important articles as well as whole subjects, e.g., diseases of the liver, have had to be omitted.

ESOPHAGUS

Attention paid to the esophagus in recent years has been increasing. The extent of current interest in this viscus is indicated by several recently published comprehensive monographs (1, 2).

Cardiospasm and Disordered Motility

The interest of internists, radiologists, and clinical physiologists in cardiospasm has stimulated considerable investigation of the function of the esophagus, both normal and abnormal. The review by Code *et al.* (3) of recent work on this subject indicates that the earlier balloon kymographic studies of Kramer and Ingelfinger, the roentgenologic studies of Templeton, and the pressure measurements of the Mayo group are in substantial agreement. Normally, primary peristaltic waves, initiated by swallowing, start in the esophagus and traverse its entire length, thus serving to transport the bolus of food; secondary peristaltic waves, initiated by distention, start at the level of the aortic arch and empty the esophagus of its contents; and tertiary waves occur chiefly in the lower third of the esophagus. In contrast, patients with cardiospasm exhibited abnormal motility or abnormal responses to swallowing. Although all such subjects displayed spontaneous waves of motility, these failed to propel either a balloon or a food bolus; swallowing induced primary peristaltic waves only rarely, and secondary waves were shallow, uncoordinated, and purposeless. Such complementary studies suggest that the defect in cardiospasm involves the entire motor apparatus of the esophagus, not merely the cardiac sphincter as has often been believed. It is tempting, therefore, to identify this defect with the absence or loss of ganglion cells in the esophageal wall, an observation of long standing and recently verified several times. Indeed, the abnormal tonic contraction of the esophagus following methacholine (Mecholyl) in patients with cardiospasm, observed by Kramer and Ingelfinger and confirmed by Code *et al.*, has been

[1] The survey of the literature pertaining to this review was completed in July, 1953.

interpreted as being in keeping with this absence of ganglion cells, in accordance with Cannon's law of sensitivity of denervated structures.

Current surgical measures for treatment of cardiospasm are valuable in relieving esophageal delay or obstruction at the cardia, but they present the serious risk of postoperative complications as a result of reflux of gastric juice into the esophagus. The danger of postoperative peptic esophagitis and ulceration with bleeding is emphasized by several recent reports (4, 5). The best approach appears to be offered by the Heller type of operation, cardiomyotomy, since it interferes less with the "cardiac sphincter" than do any of the other procedures.

Although the respiratory symptoms of cardiospasm have been known for a long time, Andersen *et al.* (6) emphasize the occurrence of significant pulmonary complications in many patients with this disorder. Aspiration pneumonitis was the most common finding and probably the basis for chronic structural changes in the lungs seen in some cases, thus stressing the need for early correction of the basic defect in cardiospasm.

BLEEDING ESOPHAGEAL VARICES

Emergency treatment of bleeding varices by variations of balloon tamponage continues to undergo evaluation. Thus, in one series of 37 patients treated with the Blakemore-Sengstaken esophageal tube, major bleeding was arrested in 21 cases, yet 15 of the group died (7). Linton (8) has advocated cardioesophageal tamponage by intragastric balloon traction plus transesophageal suturing of the varices, because of the technical difficulties presented by esophageal tamponage. Definitive surgical treatment of varices, however, must of necessity be done when the patient is not bleeding. Such treatment may be effected by either of two types of venous anastomosis available for reducing portal pressure: splenorenal or portocaval shunts. The effect of these anastomoses on portal pressure has been shown by Palmer *et al.* (9) by direct measurement of variceal pressures, through a direct puncture with the esophagoscope in cases where the varices persisted postoperatively.

STOMACH

The importance of the physiological basis of renal and cardiovascular disorders has long been recognized in internal medicine, but for the gastrointestinal tract such recognition is only recent. An important landmark in this connection is the series of seminars in gastrointestinal physiology in the *American Journal of Medicine* during 1952. The paper by Code *et al.* (3) already cited, and the review by Quigley & Brody (10) on intraluminal pressures make a splendid introduction to the motor aspects of gastrointestinal function. The reviews by the present authors present their point of view on gastric secretion (11) and the limitations as well as value of function tests (12).

CARDIO-ESOPHAGEAL FUNCTION

Discussions on hiatus hernia continue to center around the esophagogastric junction. The radiographic demonstration of reflux of gastric contents

into the lower esophagus has lent support to the idea that this phenomenon plays a major role in the pathogenesis of "heartburn," in reflex peptic esophagitis associated with duodenal ulcer, and in peptic ulcer of the esophagus associated with hiatal insufficiency or true hiatus hernia. A noteworthy series of 130 patients with hiatus hernia treated surgically has been reported by Sweet (13); 89 per cent had the sliding type of hernia, 5 per cent parahiatal hernia, 2 per cent a composite of these two forms, and 4 per cent a true short esophagus. Pain, bleeding, and obstruction were the most frequent indications for surgery. All cases were repaired transthoracically, with no recurrence of bleeding and only four proven recurrences of the hernia.

Transpyloric Prolapse of the Gastric Mucosa

Strongly contrasting points of view continue to be presented concerning the significance of transpyloric prolapse of the gastric mucosa. The incidence of this finding in routine roentgen examination varies extensively in several recent reports: 1.8 per cent in one series of 20,467 examinations (14), 5 per cent in a group of 150 cases (15), and 15.5 per cent in 1000 consecutive examinations in a third series (16). The roentgenographic criteria for the diagnosis of prolapse have been reviewed by Feldman *et al.* (14) who point out that it occurred in 14 per cent of their patients with gastrointestinal symptoms. Rappaport *et al.* (16), noting (*a*) that this condition often occurs in patients with no symptoms and (*b*) that surgery occasionally fails to relieve symptoms ascribed to prolapsing mucosa, are inclined to give this entity little weight, although not dismissing it completely as a factor in engendering symptoms. Fundamental data on the anatomical variations in degree of looseness of the antral mucosa are needed before clinical significance can be attributed to the more marked degrees of its transpyloric prolapse.

Peptic Ulcer

The recent extensive review of Kirsner & Palmer (17) provides a balanced introduction to the problems of peptic ulcer. Emphasis upon tissue resistance as well as active gastric juice in pathogenesis of this disease reflects a point of view which agrees with our own experimental and clinical approach to these problems. Since most individuals secrete acid and pepsin but relatively few have ulcers, gastric juice may be a necessary but not the sole factor; varying susceptibility of the gastroduodenal mucosa to peptic digestion must also play a major part.

Etiology.—Numerous recent studies clearly demonstrate that patients with duodenal ulcer usually secrete more HCl and pepsin than normal individuals; in contrast, those with gastric ulcer are normo- or hypo-secretors. Many causes of this hypersecretion in duodenal ulcer have been proposed. Cox (18) has presented evidence that the mucosal density of gastric acid cells is greater in duodenal ulcer than in the normal; whereas the gastric ulcer stomach contains fewer parietal cells than the ulcer-free stomach. However, this high cell density may be a consequence rather than a cause of the hypersecretion in view of the experimental findings of Cox (18), Cambel

& Sgouris (19), and others, that histamine stimulation increases the density of parietal cells in several species of animals. The rather low incidence of gastric ulcer in the presence of hypersecretion of duodenal ulcer presents a serious problem in the light of current concepts. The incidence of coexistent gastric and duodenal ulcers has recently been reviewed by Feldman (20) and found to be low, by autopsy as well as x-ray evidence. This may be the result only of the gradient in tissue resistance between stomach and duodenum, but it may also reflect the pH-activity curve for pepsin, which indicates a lower enzyme activity at an acidity above 100 mN than at one of 25 mN.

The studies of Dragstedt *et al.* (21) on hypersecretion and ulceration in animals with the antrum transplanted to the colon, again suggest the possibility that the hormone, gastrin, underlies the mechanism for hypersecretion in duodenal ulcer patients. This is in keeping with the markedly reduced secretion following antrumectomy during partial gastrectomy, even though marginal ulcers can occur in the subtotally gastrectomized individual.

The review by Kirsner (22) of the role of hormones generally is indeed timely. Especially noteworthy is his treatment of the adrenals. Although ulcer activity and bleeding in patients receiving ACTH or cortisone have focussed attention on this gland, and the studies of Gray *et al.* have shown a stimulatory effect on ACTH on gastric secretion, evidence for an association of cortical hyperactivity and duodenal ulcer is lacking. It is significant also that the endogenous hyperactivity of the adrenal cortex in Cushing's disease is rarely associated with peptic ulcer. More striking, but quite inexplicable, is the relation betweeen ulcer and certain phases of sexual function. Clark (23) has presented anew evidence that ulcer symptoms disappear in 90 per cent of women during pregnancy, and that a significantly large proportion of ulcers start or flare up, or undergo complications at the menopause.

Diagnosis.—It has been known for many years that a portion of the pepsinogen secreted by the stomach finds its way into the urine, i.e., that the activity of the peptic cell is endocrine as well as exocrine, and there is a good correlation between the outputs of gastric and urinary pepsinogen under basal conditions. Further, Mirsky and his colleagues and the present writers have shown clear-cut elevations of urinary pepsinogen excretion above the normal in duodenal ulcer patients, but not in those with gastric ulcer or carcinoma. The use of such urinary pepsinogen determinations for diagnosis in ulcer disease has been reported by Eastcott *et al.* (24) and by Hirschowitz (25). The latter found a good correlation between urinary pepsinogen in duodenal ulcer and duration of the disease. The use of this determination in the patient with gastrointestinal bleeding, where gastric intubation is contraindicated, has been suggested. Since pepsinogen finds its way into the urine from the stomach, it was logical for Mirsky *et al.* to direct their attention to blood pepsinogen also. They have found (26) that human plasma contains two proteolytic enzymes of nongastric origin in addition to a pepsinogen-like system, active at pH 1.5 to 3, and never present in the absence of a functioning gastric mucosa. Results with their new method for assay of this third

component (27) were consistent with previous urinary studies: plasma pepsinogen was significantly higher in patients with duodenal ulcer, and significantly lower in those with pernicious anemia than it was in apparently healthy subjects of the same age.

For some years, interest in electrical phenomena associated with gastric secretion and motility has been increasing. In the most recent attempt to use such measurements diagnostically, Martin & Morton (28) have shown that the normal electrogastrogram has AC components as well as a dominant DC component. Large, exceedingly slow waves may be associated with nausea, whereas drinking increases the negative resting potential. Recordings in the presence of peptic ulcer are strikingly different from the norcordings in the presence of peptic ulcer are strikingly different from the normal picture. In cases of gastric malignancy, characteristic changes suitable for diagnostic purposes were not observed, although previous reports of their occurrence have been published.

Medical therapy.—Much effort is being directed to the evaluation of newly synthesized gastric antisecretory drugs of the anticholinergic group. If we accept Kirsner & Palmer's (29) definition of an ideal antisecretory drug as "a safely administered compound that consistently inhibits the output of HCl for long periods, after oral ingestion, without the development of tolerance and with minimal or no side effects," then the ideal compound has not yet been synthesized. These authors have evaluated a large number of substances in terms of their ability to inhibit continuous acid secretion in patients with duodenal ulcer and found wide individual variations in their antisecretory activity. The more potent agents tended to produce more side effects, and none of them consistently produced anacidity in man without some disturbances. Nevertheless, the authors conclude that the outlook for the synthesis of still more effective drugs is good. Reports on Antrenyl (30), Prantal (31), methantheline (Banthine) (32), as well as antisecretory drugs still in the experimental stage (33), continue to appear. In contrast to the optimistic tone of earlier studies, there appears to be emerging a sense of the limitations of these preparations (34). Although, when given alone, their effect on pain is striking, they fail to prevent any considerable degree of ulcer recurrence.

The usefulness of these drugs in the relief of pain has prompted reinvestigation of the perennially interesting problem of ulcer pain per se. Palmer *et al.* (35) have reported that anticholinergic drugs do not affect the perception of such pain. In 23 of 26 trials, pain could be induced by instillation of acid after the anticholinergic drug was given. The relief of pain in duodenal ulcer clinically is explained by delay in gastric emptying and diminished acid secretion, thus decreasing the exposure of the crater to acid rather than to any direct effect on pain production. Hightower & Gambill (36), on the other hand, correlated the recognition of pain with the occurrence of type II antral contractions and attributed its inhibition by methantheline to the inhibition of these contractions. Ruffin *et al.* (37) interpreted their re-

sults to mean that ulcer pain is invariably associated with abnormal gastro-duodenal motility and ascribed its relief by anticholinergic drugs to inhibition of such motor activity. These reports do not rule out the role of HCl, nor clearly distinguish its role from that of abnormal motility.

The metabolic risks of excessive alkali in the therapy of ulcer are pointed up by the report of Becker *et al.* (38) on renal parenchymal calcification in patients with chronic ulcer. Such calcification was demonstrated in 36 per cent of 99 ulcer cases at autopsy, compared to 13 per cent in a comparable control group. The authors suggest that the renal lesion arises from large intake of Ca in the diet and transient episodes of alkalosis. The metabolic disturbances in certain duodenal ulcer patients, previously described by Burnett *et al.* in 1949, in which metastatic calcification, hypercalcemia without hypercalcuria or hypophosphatemia, and renal insufficiency occurred, were seen in six ulcer patients with excessive intake of milk and alkali. A case has been reported this year by Wermer *et al.* (39) in which metastatic ocular and subcutaneous lesions regressed following dietary restriction of Ca, although the patient subsequently died in renal failure. No case of this syndrome has been seen in which excessive milk or excessive alkali alone were consumed.

Surgical therapy.—Papers on the relative merits of subtotal gastric resection, gastroenterostomy, and vagotomy alone, or in combination with one of the other procedures, occur in the literature with a frequency too great to permit of individual discussion. Even when amply supported by the surgeons' own experience, statistical studies are often inadequate because of relatively small groups of patients, selection of cases, and impossibility of comparing different operative procedures because data on only one variety were available. For this reason, the American Gastroenterological Association undertook a critical nationwide statistical study of several procedures for duodenal and gastrojejunal ulcer. A special committee, aided by a reputable statistician, collected data on more than 5200 patients from 121 hospitals in the United States and Canada (40, 41). Chief among its many conclusions are the following: (*a*) The common surgical opinion that, for gastric ulcer, resection alone is adequate was accepted without investigation. (*b*) For duodenal ulcer, vagotomy, alone or combined with pyloroplasty, is significantly inferior to vagotomy combined with gastroenterostomy or gastric resection. (*c*) The addition of vagotomy to partial resection for duodenal ulcer yields no improvement in the therapeutic result during the first few postoperative years. However, a higher incidence of histamine achlorhydria after the combined operation may possibly reduce the chance of later recurrence. (*d*) The results of vagotomy plus gastroenterostomy for duodenal ulcer are not essentially better than those for gastroenterostomy alone. However, in patients with a gastrojejunal ulcer, particularly following gastric resection, the addition of a vagotomy is likely to be of definite benefit. Gastric resection instead of vagotomy in such cases is likely to be even more successful. (*e*) Partial resection alone, particularly of more than 70

per cent of the stomach, is superior to gastroenterostomy with or without vagotomy. The report is noteworthy for its discussion of the difficulties encountered in any large scale clinical-statistical study of this kind. In spite of the large number of patients included in the survey, some of the data are so meager as to be valueless for rigorous statistical comparisons. This is particularly true for the quantitative data of the several function tests which are known to give significant information. In spite of the statistical limitation inherent in many reports on individual surgical experiences, some of these are significant. Thus, Druckerman *et al.* (42) conducted a comparative study of partial gastrectomy with and without vagotomy in 550 patients, with results essentially in agreement with those of the nationwide survey.

The postgastrectomy symptom complex labeled the "dumping syndrome" remains a focal point of continuing investigation. Pontes & Neves (43) present evidence that the stress of this disorder invokes adrenal cortical stimulation, perhaps by way of epinephrine release. Glazebrook & Welbourn (44) ascribe the syndrome in part to increased motor activity of the small intestine rather than to distention of the jejunum per se. The administration of penta- and hexa-methonium salts resulted in pronounced reduction in motor activity and symptoms, but therapeutic trials with these drugs reduced postprandial symptoms in only 4 of 12 cases.

The widespread use of subtotal gastrectomy for ulcer disease, markedly increasing in the younger age group, has led to the recognition that this operation can sometimes induce a nutritional handicap. Numerous reports, summarized by Everson (45), indicate that a significant number of these patients remain asymptomatic except for an inability to regain weight, and others continue to lose. In a tabulation of metabolic balance studies on such gastrectomized subjects, previously published, fat assimilation was impaired in 23 of 36 patients, and protein in 11 of 44 cases studied. Everson suggests the following factors as responsible: (*a*) loss of digestive function of the stomach, (*b*) loss of triturating function, (*c*) decreased stimulation of pancreatic and biliary secretions, (*d*) improper mixing of food with bile, (*e*) increased intestinal motility, and (*f*) loss of the gastric reservoir function. Loss of weight may result from inadequate intake of food, rather than failure to absorb fat. This is suggested by Welbourn *et al.* (46) who investigated the loss of fecal fat in dogs subjected to a variety of gastric operations. Partial (50 to 70 per cent) gastric resection increased the fecal fat content only slightly when these animals received a diet of 16 per cent fat, but total gastrectomy increased it markedly. Vagotomy added to partial gastrectomy had no consistent effect. Loss of weight in these dogs was caused more by inadequate intake than by excessive loss of food.

GASTROINTESTINAL BLEEDING

A more energetic approach to the management of massive gastrointestinal hemorrhage has led to a reevaluation of its pathological basis. Chalmers *et al.* (47), in an instructive clinicopathological correlation of 101 fatal cases

of massive bleeding, found 74 instances of a single probable source of bleeding at autopsy, 20 with multiple sources, and only 7 where none was demonstrable. The two main groups of bleeders comprised 50 peptic ulcers and 32 esophageal varices. Of the 50 ulcer patients, 23 had grossly visible bleeding points, but in only 3 was there a large gaping sclerotic pancreaticoduodenal artery, so frequently assumed to be the source of massive bleeding.

The development of emergency therapy of hemorrhage requires emergency diagnostic methods. Zamcheck *et al.* (48) have performed a needed service in their study of emergency roentgen examination of the gastrointestinal tract in 123 severely bleeding patients, the majority of whom were examined within two days of hospital admission. Pressure was used in 43 of these patients and omitted in 47; 13 were examined in recumbency only. Although bleeding occurred in 12 cases at some time after completion of the examination, the results indicate that such emergency x-ray studies can be performed safely, without a single fatality attributable to the procedure. Anatomical verification indicated a high degree of reliability of this diagnostic procedure, but multiple pathological findings added to the complexity of management in these 53 patients. For this purpose, an integrated team of internist, surgeon, radiologist, clinical pathologist, blood bank directory, and anesthetist is necessary (49, 50). Also, an aggressive approach is essential, since there is still a significant mortality rate in patients over 50 years of age with massive bleeding, despite the liberal use of early feeding, intravenous fluids, and blood. Advocates of emergency subtotal gastrectomy point out that the mortality rate following this procedure is lower than after conservative management, at least in older patients (51, 52, 53). This point of view is gaining adherents, but it still represents a minority attitude (54).

MALIGNANT TUMORS OF THE STOMACH

Statistical reports give continuing evidence that the alimentary canal is the most common site of malignancy, except for the female reproductive organs. Hence, the National Advisory Cancer Council of the United States Public Health Service sponsored another of its conferences on Gastrointestinal Cancer in 1952. Most attempts to determine the cause of adenocarcinoma of the stomach reflect the hypothesis that the gastric mucosa is susceptible to attack by carcinogens, particularly of dietary origin, at its lumenal surface. Among such agents are overheated fats, and the rodent studies of Roffo gave support to this suspicion. However, similar attempts by Peacock *et al.* (55) and others have failed to confirm Roffo's observations, although they all result in squamous tumors in the nonglandular forestomach. Analogous studies with synthetic carcinogens, applied topically to an explant of rat gastric mucosa, have also been unsuccessful (56). Interest in the gastric mucous barrier as a possible protective agent against ingested carcinogens, is indicated by four reports on various aspects of the chemistry and physiology of the mucous barrier (57 to 60). An excellent statistical study of the incidence of gastric cancer is that of Gardner *et al.* (61), in which its occurrence

in a group of parents and siblings was 2 1/2 times that of the general population; cancer of other organs did not show such a difference in frequency.

The relationship of gastric ulcer to gastric cancer continues to be a grave problem, not because of the possibility of malignant degeneration, but because of the difficulty of differential diagnosis. Horn & Ravdin (62) report that 11 per cent of 101 patients who came to surgery with a diagnosis of gastric ulcer proved to have a malignancy, and 25 per cent of 52 supposedly cancerous patients had a gastric ulcer. On the other hand, Brown *et al.* (63), using "strict criteria" for the diagnosis of gastric malignancy, found only eight cases (1.1 per cent) in a series of over 700 routine autopsies. It is interesting that these two percentages, 11 and 1.1, represent almost the entire range of incidences previously reported on the subject.

The long-standing use of achlorhydria for diagnosis of gastric malignancy is being subjected to serious question. The incidence of achlorhydria is usually compared in patients with and without gastric cancer. Berkson & Comfort (64) consider such control patients as a "selected group" and therefore not a random sample of the general population. Hence, they studied the histories over a 10-year period of a group of patients with achlorhydria but not cancer. The frequency of gastric malignancy in this group was not essentially greater than that expected from the general nonhospital population. Furthermore, current data on the diagnostic use of achlorhydria in suspected malignancy of the stomach suggest an incidence of 50 to 69 per cent, but adjustment for the spontaneous loss of secretory function with age is frequently lacking.

Mass screening for cancer diagnosis continues to gain momentum. Because of the difficulties of gastric intubation, tubeless methods for detection of achlorhydria are attracting increasing attention. The use of quininium cation exchange indicator substance (Diagnex), which is excreted in the urine only if free HCl is present in the stomach, has again been reported on by its inventors, Segal *et al.* (65), and statistical evidence of its reliability is presented. Other workers have also found this useful in detecting achlorhydria (66, 67). Almost 5100 people with essentially no gastrointestinal complaints have been screened by photofluorography by Wigh & Swenson (68) over a period of several years. This group presented 11 gastric neoplasms, several 1 cm. or less in diameter. A similar study by Sloan *et al.* (69) on 10,000 dispensary patients (having some symptoms prior to examination) revealed a minimum of 35 cases of proven malignancy, 24 unproven but potential malignancies, and 96 benign lesions about one-third of which were confirmed.

Even more promising for mass screening is cytologic diagnosis involving gastric aspirates. Because of the high incidence of false negatives, when their method involved aspiration without abrasion of the gastric mucosa, Cooper & Papanicolaou (70) have now instituted an abrasive balloon technique to aid desquamation. In 238 cases, of which 51 were proven malignancies, there were 38 correct positive reports, 7 suspicious, and 6 false negatives; and of 187 cancer-free subjects, there was 1 false positive and 9 suspicious of gastric malignancy. Traut *et al.* (71) have been using gastric lavage with

papain prior to aspiration, to hydrolyze the gastric mucin and so obtain smears richer in cell content. In 400 patients examined with papain pretreatment, the diagnostic accuracy was 85 per cent in contrast to only 51 per cent in 600 patients similarly lavaged with saline. The percentage of false positive reports is also decreased by papain lavage.

Regarding surgery for gastric carcinoma, optimism persists in spite of poor results. Extensive resections are being performed with far greater frequency and a far lower mortality than 10 years ago, and Horn & Ravdin (62) urge that every gastric ulcer be resected. Similarly, Ochsner & Blalock (72) believe it imperative that exploration be performed in all men past 40, who have been entirely well previously and in whom the first onset of digestive disturbances persists in spite of conservative therapy. Wangensteen also (73) is continuing to reoperate upon those patients in whom primary resection of a wide margin of normal tissue with the cancer revealed the presence of cancerous regional lymph nodes (the "second-look" procedure).

PERNICIOUS ANEMIA

Attempts to understand the association of Castle's intrinsic factor with the mucous secretions of the alimentary canal occupy a prominent place in the year's activities. Landboe-Christensen *et al.* (74) have reported that extracts of human duodenal tissue contain moderate amounts of intrinsic factor, relative to similarly prepared extracts of fundus mucosa; jejunal preparations were inactive. Whether the active material is native to the duodenal tissue or merely represents intrinsic factor of gastric origin which has been adsorbed by duodenal mucus could not be established. Glass (75) has shown that his "glandular mucoprotein," obtained from the gastric juice of individuals free of pernicious anemia, acts as a potentiator of the hematopoietic activity of vitamin B_{12} when administered orally. But again it has been impossible to state whether this product of the mucous cells is identical with the active agent or merely carries it as an adsorbate. Even electrophoresis has failed to separate the intrinsic factor from contaminants in human acid juice. Filter paper electrophoresis yielded several peaks, all of which possessed vitamin B_{12}-building activity. Material from two of these peaks, from the anodic and cathodic sides respectively, was effective clinically against pernicious anemia.

SMALL INTESTINE
INTESTINAL FUNCTION TESTS

Tests of intestinal function, both secretory and motor, have been reviewed by Janowitz (12). Their limitations offer a striking challenge to the clinical investigator. Chapman *et al.* (76) studied the effect of several drugs on propulsive movements radiographically. They felt that the barium meal technique is a useful one for this purpose and their results are in essential agreement with those of previous balloon studies with drugs. Methantheline (100 mg. orally) caused a more striking decrease in intestinal transport and in the delay of gastric evacuation than belladonna or a placebo.

Of the two kinds of absorption tests used at present, (*a*) balance studies are time consuming, costly, require a high degree of patient co-operation, and are not suitable for the study of carbohydrates since these may be destroyed by bacterial fermentation; and (*b*) tolerance tests, based on systemic blood concentrations, are influenced by factors which remove substances from the blood, as well as by intestinal absorption. Consequently, all attempts to devise or improve methods for more direct study of absorption are worthy of note. Cummins (77) has studied the absorption of glucose and methionine in man by a variant of the method of Nicholson and Chornock. In this, the compound is dripped into the intestine, travels down with the normal bowel current, and is aspirated below, loss being prevented by an occluding balloon. Using a 45 cm. segment of upper small bowel, Cummins noted considerable variability in result between two consecutively run tests in seven subjects; variations were under 25 per cent for glucose and under 50 per cent for methionine. His results indicate that glucose absorption is influenced by its concentration within the gut, in contradiction of "Cori's law," and it is not affected by venous infusion of glucose or lowering blood sugar with insulin. He concluded that the chief use of the procedure seemed to be in studies of those influences on absorption which vary between two consecutively performed tests. Taylor & Wightman (78) used a similar input and recovery technique, with balloon occlusion of the gut, to study glucose absorption in human subjects, and the method merits further application.

GRANULOMATOUS REGIONAL ENTERITIS

In the 21 years since this disease was identified as a clinical and pathological entity, the one important addition to the clinical picture is the concept that the condition is not restricted to the terminal ileum, but can involve the entire small bowel. With the 1950 paper of Comfort *et al.* it became clear that the stomach and duodenum can also be involved, and this year two more cases of granulomatous disease in the stomach, similar to regional enteritis, have been reported by Martin & Carr (79). In the absence of etiological similarity, the identity of these disease processes, involving different levels of the digestive tract, must rest on the similarity of their histological pictures. The characteristic granulomatous epithelial cellular reaction with giant cells is well known, especially the involvement of regional lymph nodes of regional lymphatics. Warren & Sommers (78a) have stressed the absolute distinctness pathologically of the granulomatous enteritis lesions from those of ulcerative colitis.

A vexing problem is whether the chronic granulomatous disease is preceded by an acute stage. Crohn, in his monograph on the subject, found a lack of evidence upon which to base a definitive answer. It is of interest, therefore, that Storrs & Hoekelman (80), from their study of acute regional enteritis in children, believe that their eight patients healed completely, none going on to chronic involvement; in seven of these, the follow-up ranged from 3 to 13 years.

Whereas the psychosomatic aspects of ulcerative colitis are clearly recog-

nized, experienced observers do not agree on the role of psychological factors in regional enteritis. However, Grace (81) closely correlates the onset of the illness and of each exacerbation with periods of stressful life situations in four cases.

In view of the effectiveness of ACTH and cortisone in controlling some granulomatous disease processes, including sarcoidosis, it was to be hoped that these agents would prove a major contribution to the therapy of regional enteritis. The disappointing experiences of Sauer *et al.* (82) and others conform with the majority of reports involving considerable numbers of patients. In 12 cases of regional enteritis treated with ACTH, it was impossible to demonstrate any objective evidence of sustained improvement; esophagitis. psychosis, and perforation of the ulcerated intestine were serious complications.

THE SPRUE SYNDROME

Therapeutic interest in sprue has been stimulated by the recent demonstration by several groups of investigators that ACTH and cortisone have beneficial effects on some refractory cases. Absorption in nontropical sprue has been carefully and impressively studied by Comfort, Wollaeger, and others at the Mayo Clinic for many years by the balance technique, and a recent report (83) summarizes some of their metabolic studies on the apparently generalized defect in absorption in this syndrome. In addition to the well-known loss of fecal fat, fecal nitrogen was elevated in many patients so that the latter could not be used in differentiating sprue from external pancreatic insufficiency. Fecal values for Ca, P, Cl, Na, and K tended to be higher than the average values reported for normals. Balances for all these elements may be negative during periods of exacerbation. Usually, the greater the fault in fat absorption the greater was the absorptive defect in nitrogen and minerals, but there was no exact parallelism between the two, nor between fat and nitrogen losses. The defect may be an over-all one rather than one related only to fat absorption, as has been widely thought in the past.

Taylor & Wightman (78) have given further evidence of a defect in glucose absorption, by the method of recovery of intraduodenally instilled glucose. The impairment was reflected also in flat oral glucose tolerance curves. Cummins & Almy (84) used the same method (77) to study the role of motility in absorption in two sprue patients and three normal individuals. Intestinal motility, increased with bethanechol (Urecholine) and physostigmine, augmented the absorption of glucose and methionine, but hypomotility induced with methantheline did not alter the shape of the glucose tolerance curves when the sugar was introduced directly into the duodenum. The authors properly draw the cautious conclusion that the hypomotility of the bowel in sprue is probably not the sole or even primary cause of the poor absorption of glucose. They speculate that the increase in absorption, induced by increasing intestinal motility, may be attributable to an associated increase in intestinal blood flow. This study indicates the need for correlating

intestinal motility with all studies on absorption.

The older studies of Verzar on the role of the adrenal in intestinal absorption, and the therapeutic results with cortisone have stimulated anew the study of the adrenals in the sprue syndrome. Rivas et al. (85) presented evidence that adrenal insufficiency may be involved in tropical sprue: i.e., impaired water tolerance tests, low 17-ketosteroid excretion, and inadequate eosinopenic response to ACTH. The adrenals, studied in 13 necropsies, revealed a variety of changes ranging from depletion of cortical lipids to edema and lymphocytic infiltration. Patients with sprue do have episodes of curious electrolytic imbalance, suggestive of Addison's disease, but there is no evidence of adrenal insufficiency in carefully studied cases of nontropical sprue; evidence from the adrenal function tests above is fragmentary, and the post mortem changes may have resulted from nonspecific stress.

Although less than 50 cases of Whipple's disease (lipophagic granulomatosis intestinalis) have been reported, much interest has been shown in this form of the sprue syndrome, since it appears to have a clear-cut histopathologic basis. Upton (86) has confirmed a finding, known for several years, that the characteristic foam cells of the enteric mucosa contain a mucoprotein, rather than a lipid, as judged by histochemical staining methods. This was known in part by Whipple himself since he commented on the failure of some of the foam cells to take the osmic acid stain. This may also be correlated with the recent observation that the serum mucoprotein is elevated in this disease.

MASSIVE RESECTION OF THE SMALL BOWEL

The ability of the organism to adapt to the loss of large areas of intestinal absorptive surface is of more than physiological interest, not only because of the occasional patient with vascular lesions who undergoes emergency resection, but because extensive resection for diffuse inflammatory disease of the small bowel is being attempted currently. Jackson & Linder (87), in a careful metabolic and clinical study of a man surviving with seven inches of small intestine, have carefully reviewed previous experimental and clinical reports of extensive small bowel resection. They cite the early work of Flint with dogs who showed hypertrophy of the intestinal villi following excision of up to 80 per cent. Clatworthy et al. (88) have repeated some of these studies in 19 puppies by resecting 40 to 80 per cent of the small intestine distal to the ligament of Treitz, without impairment of growth or development. These animals also developed hypertrophic changes in the intestinal villi, and an increase in caliber of the bowel itself. Jackson and Linder's "Toni," who survived for more than two years, manifested a large loss of protein, PO_4, Ca, Na, and Cl in the feces, and almost complete absence of fat absorption. Of interest was the temporary retention of salt and water, with their excretion after some delay and mostly at night. Interesting metabolic studies of individual patients for varying periods of time following resection of most of the small bowel have been made by Kozoll et al. (89) and Spencer et al. (90).

COLON AND RECTUM

Congenital Megacolon (Hirschsprung's Disease)

The entire concept and treatment of congenital megacolon has been clarified by the finding that the spastic lower sigmoid and rectum are the primary sites of the pathology of this disorder and can be correlated with the complete absence of ganglion cells from the myenteric plexus in the spastic distal portion of the colon. The success of the operation devised by Swenson and colleagues depended upon this clarification. An important and unique contribution to this problem has been reported by Kamijo *et al.* (91), who subjected the resected spastic and hypertrophied segments of colon of four patients to pharmacological and histochemical analysis. Both specific and nonspecific cholinesterase activities were considerably higher in the spastic (distal) than in the hypertrophied (proximal) portions. This was associated with a large number of nonmyelinated nerve fibers in the ganglion cell-free myenteric plexus. These fibers appear therefore to be cholinergic and postganglionic. Although the current widely accepted concept is that the primary factor in megacolon is agenesis of ganglion cells in the distal spastic portion, these authors offer another interpretation of their findings. They suggest that cholinergic ganglion cells are present but outside the colon, centrally displaced, and that their postganglionic fibers extend to their usual cites of termination, in the presence of a paucity of adrenergic inhibitory neurons. Their approach to the experimental study of this disease is very stimulating, in view of Klinge's failure to reproduce the disease in cats by excision of plexuses. However, Kamijo and his coauthors emphasize the possible importance of species differences in this kind of study.

Chronic Ulcerative Colitis

Etiology.—The recent review by Machella (92) is a judicious presentation of the variety of problems involved in ulcerative colitis. The major problem remains that of etiology, and this author places much emphasis on psychic factors and the role of lysozyme in production of the disease. Interest in lysozyme has persisted ever since Meyer demonstrated its high titer in stools of patients with active ulcerative colitis. Subsequent studies have indicated that this elevated titer may be a reaction to injury rather than a primary factor, i.e., the presence of lysozyme in granulation tissue of extracolonic origin, and the failure of lysozyme to liquify colonic mucus both *in vivo* and *in vitro*. Hiatt *et al.* (93) have presented evidence in keeping with observations of previous workers, that the granulocyte of the colonic inflammatory reaction is the source of the lysozyme in ulcerative colitis.

Therapy.—Machella (92) has culled from the literature 117 cases treated with ACTH (79 patients improved) and 25 patients treated with cortisone (11 patients improved). All observers have been impressed with the ability of these hormones to induce striking symptomatic remissions in some patients and with their value as adjuvants to the conventional handling of this disease. Whereas Brown & McAuley (94) stress the need for larger doses

and longer schedules of treatment with cortisone, Tulin *et al.* (95) offer a cautionary note in their report of 17 patients treated with ACTH, in 3 of whom there occurred perforation of the colon, with localized peritonitis in one and generalized peritonitis in 2 (one death). It would seem that, in the presence of acute fulminating deeply ulcerating or bleeding colitis, use of these compounds is hazardous. Morrison (96) reported a three-year study of 60 patients, treated with salicylazosulfapyridine successfully and was encouraged to investigate it further. However, Machella's table indicates that the results with this compound are probably no different from those obtained with other sulfonamides or antibiotics.

In the surgical treatment of colitis, Crile (97) has urged ileostomy and simultaneous subtotal colectomy. Decision regarding surgical intervention must of necessity be influenced by the continuing evidence (92) that the incidence of a carcinoma in long-standing ulcerative colitis is significant.

Extracolonic aspects.—Uyeyama *et al.* (98) have demonstrated disturbances in intestinal absorption in patients with ulcerative colitis. The rate of vitamin A absorption was reduced and was restored towards normal when a favorable therapeutic response to ACTH or cortisone was achieved. In the authors' opinion, the disturbed absorption cannot be ascribed to hypermotility of the small bowel, although this was present in their subjects. Emulsifying agents had no effect on the abnormal vitamin A tolerance curve. Flattened methionine absorption curves in colitis are ascribed to rapid utilization of amino acids. Curiously, galactose absorption was found to occur at twice the normal rate, and appeared to be correlated with intestinal hypermotility. The basis for these absorptive defects is not clear.

Histological evidence of a high degree of liver involvement in ulcerative colitis is furnished by Kleckner *et al.* (99). These workers performed needle liver biopsy in 32 patients with ulcerative colitis, 26 of whom had clinical or laboratory evidence of hepatic dysfunction. Of the 6 patients without such independent evidence, only 2 showed normal hepatic tissue, whereas of the other 26 only 3 biopsies were normal. The relationship of these findings to the nutritional disturbances or toxemia of the underlying colitis is problematic.

Of all the extracolonic factors affecting ulcerative colitis, pregnancy is perhaps one of the most interesting and complex. Recent publications, summarized by Machella (92) and Kallet (100), indicated that pregnancy occurring during an active phase of the disease may result in exacerbations in 40 to 50 per cent; 30 to 35 per cent of patients experience remissions. Pregnancy occurring in an inactive phase of the disease reactivates the condition in about 40 per cent of women. Such exacerbations during pregnancy or shortly after delivery may be extremely severe and difficult to manage, and rectoanal complications may be very stubborn. Effects of pregnancy in colitis have usually been interpreted in the light of psychosomatic concepts. However, the possible endocrine relationships involved require investigation, especially since there appears to be also a definite association of remission of ulcerative disease of the stomach and duodenum with pregnancy.

AMEBIASIS

Despite the constant injunction of those dealing with amebiasis, that the disease is far more widespread than is recognized, continuing reports reveal that it had not been considered as a diagnosis in many severe cases of the disease. Radke (101), in a study of 68 fatal cases with adequate clinical data to indicate that the primary cause of death was amebiasis, found an incorrect clinical diagnosis in 76 per cent. Peritonitis was most frequently encountered (53 per cent), with liver abscess next (43 per cent), and pleuro-pulmonary involvement third (4 per cent). Only 2 of the 42 cases with liver abscess were without lesions of the large bowel, and one had been treated specifically. This author emphasizes the fact that cysts of *Endoamoeba histolytica* were reported as having been seen by others in the tissues of five autopsy specimens and by him in many more, suggesting that the concept that "cyst-passers" do not have the disease ought to be abandoned.

New modifications of the complement fixation test for diagnosis of amebic disease continued to be presented. Although Steigmann *et al.* (102) found the test worthy of further clinical evaluation, the results of an extensive study by Buchman *et al.* (103) were quite discouraging. In 63 cases of amebiasis, proved by finding the organism in the stools or at sigmoidoscopy, only 24 had positive fixation tests. In a control group of 553 unselected patients, 47 individuals gave positive tests, yet only one could be proven to have the disease. It is this high incidence of false positives which, in the authors' opinion, precludes the use of this test for screening.

The therapeutic efficiency of the new amebicidal drugs has been recorded by many authors; two are cited (104, 105). The combination of bismuth glycolyl arsanilate (Milibis) and chloroquine (Aralen) has been extensively used with initial good results, but longer follow-ups are needed. The efficacy of wide spectrum antibiotics alone has proved disappointing.

CARCINOMA OF THE COLON AND RECTUM

In contrast with gastric cancer, the outlook in carcinoma of the large bowel is much more optimistic. Thus, White (106), reviewing 241 patients followed for at least five years after resection for this disease, reports a post-operative mortality of 9.5 per cent, and a five-year survival rate of 60 per cent. Important factors influencing the outcome were grade of malignancy, involvement of regional lymph nodes, extent of resection, early diagnosis, and recognition that polyps of the colon are premalignant lesions. Thus Welch *et al.* (107), in reviewing records of 372 patients operated upon for papillary adenomas or adenomatous polyps, found 18.6 per cent who had malignant cellular changes. When it is realized that three-fourths of the polyps can be seen with the sigmoidoscope, the use of sigmoidoscopy in case searching or in routine physical examination seems clearly indicated.

There is a growing recognition of a high incidence of local recurrence at the site of anastomosis in resection for cancer, in contrast to the low recurrence rate of those operations where no anastomosis is performed (abdomino-perineal resection). Cole (108) reports a local recurrence rate of 16 per cent

among 55 patients with resection for cancer. Of these 9, there were 6 with recurrent lesions at the suture line, suggesting that the local recurrence may be attributable to implantation of live cancer cells either displaced by manipulation during the operation or desquamated from the tumor into the lumen before operation.

USE OF ANTIBIOTICS IN BOWEL DISORDERS

The use of the broad spectrum antibiotics often results in diarrhea, proctitis, and even ulceration, and continued effort is being made to determine some of the factors involved. Dearing *et al.* (109) have been impressed with the development of staphylcoccus enteritis following these antibiotics. They cultured *Micrococcus pyogenes* in a considerable number of instances, and found that these patients responded to erythromycin. Reiner *et al.* (110) have reported the pathological findings in five cases of severe inflammatory changes in the colon following aureomycin and chloramphenicol. Death occurred in all five, and the mucosa exhibited surface exudation and stomal necrosis. The mechanism of these extreme changes and even the minor reactions is still obscure.

BILIARY TRACT

DIAGNOSTIC RADIOLOGY

Although there have been no striking advances concerning disorders of the extrahepatic biliary system, refinements in radiographic techniques for its diagnostic examination have been substantial. In recent years, radiographic diagnosis of gall bladder disease became standardized with the use of iodoalphionic acid (Priodax), administered orally. With suitable precautions, failure of the gall bladder to visualize following a double dose of this radiopaque substance indicated a significant degree of gall bladder pathology. Development of troublesome gastrointestinal and urinary symptoms remained the only handicap, albeit a minor one. However, visualization of the biliary ducts with this or any of the other dyes occurred with the greatest rarity. The introduction of a new cholecystographic medium, iodopanoic acid (Telepaque), now offers a further advancement in technique. Recent reports of several observers indicate that this compound gives excellent visualization of the gall bladder with a significant reduction in the incidence of unpleasant side effects (111, 112, 113). The shadow is suitably dense, and visualization of the ducts occurs much more frequently than with previous media. Larger numbers of radiolucent calculi are demonstrated with the new compound, but some radiopaque stones may be obscured by an extremely dense shadow. The ability of the new medium to demonstrate some gall bladders not visualized by other compounds may result in the evolution of slightly different criteria for "normality."

CHOLELITHIASIS

Gall stone formation continues to stimulate investigation. Christensen *et al.* (114) have continued their experimental studies with the hamster,

which apparently can form stones of high cholesterol content when reared on a cholesterol-free and nearly fat-free diet. This is not surprising in view of the ability of the organism to synthesize cholesterol from acetate. The dietary supply of cholic acid did not influence stone formation, nor is it related to blood concentration of free or esterified cholesterol. Dixon & Owen (115) report three large kinships with an extremely high incidence of gall stones, and consider a familial predisposition to cholecystic disease to be plausible. The idea is intriguing, and consistent with the concept of an inborn error of metabolism in gall stone formation, but evidence is meager. In fact, there is no indication that the inborn error of cholesterol metabolism in "essential familial hypercholesterolemia" is associated with unusual incidence of gall bladder disease or stones.

The relation of gall stones to cancer of the gall bladder is also of more than theoretical interest. Howard (116) has reviewed the pertinent literature and added further cases to emphasize the fact that stones were present in most cases of cancer of the gall bladder reported. This lends support to the concept that all gall stones, clinically "silent" or not, should be removed. The analogy with surgical removal of all solitary nodules of the thyroid to prevent carcinoma is striking.

SURGERY OF THE GALL BLADDER

The patient with "silent" gall stones presents a difficult problem in management. Branch (117) agrees that the high incidence of common duct stones, the association with cancer, and the association with acute cholecystitis are all indications for removing stones whenever discovered. This is an important matter and deserves further serious consideration.

Cole (118), in a lucid survey of the diagnosis and therapy of gall bladder disease, discusses recent trends in gall bladder surgery. Among the many points treated are (a) the chemical nature of gall bladder disease, (b) the periodicity of gall bladder pain, and (c) the need to explore the common duct for stones in all gall bladder operations. In his evaluation of the postcholecystectomy syndrome, he stresses that the gall bladder is often removed in error, either because of another disease of the intestinal tract or because of deep-seated psychoneurosis. The syndrome of residual cystic stump and common duct stone must be considered. Despite widespread impressions, chronic pancreatitis is also rarely demonstrated in these individuals, as is biliary dyskinesia.

PANCREAS

FIBROCYSTIC DISEASE OF THE PANCREAS

Because of the unusually high incidence of heat prostration in children with fibrocystic disease of the pancreas, Darling et al. (119) have studied the electrolytes in the sweat of nine such children. The Cl concentration in the sweat collected from the abdominal wall after thermal stimulation was markedly higher than in controls. These authors concluded that this excessive salt loss may represent an abnormality in the sweat glands them-

selves. This may represent increased reabsorption of water within the sweat tubule. The findings are an interesting contrast to the salt retention recently described for the sweat of patients with congestive heart failure and cirrhosis of the liver.

ACUTE AND CHRONIC PANCREATITIS

The correlation of bouts of acute pancreatitis with acute alcoholism has intrigued many investigators seeking to explain the disease in terms of the external pancreatic secretion. Brooks & Thomas (120), have shown that 5 per cent alcohol fed to dogs, alone or combined with $0.1N$ HCl, or given intravenously did not significantly increase the volume or enzymatic activity of the pancreatic juice. This is in keeping with some previous studies in man.

The demonstration by several groups almost simultaneously, that acute hemorrhagic pancreatitis can be produced in experimental animals by substituting the synthetic amino-acid, ethionine, for the naturally-occurring methionine in their diets, has raised interesting possibilities in regard to nutritional factors in the etiology of this disease in man. Likewise, the pancreatic fibrosis of the South African disease, kwashiorkor, may be related to a protein deficiency of the diet. Perhaps the effect of alcohol in pancreatitis is similarly to be explained by some interference with the protein or other metabolism of the pancreas. It is of interest that acute pancreatitis is part of the clinical picture of acute methyl as well as ethyl alcohol poisoning.

Management of acute pancreatitis presents many problems, even when conditions requiring exploratory surgery can be ruled out. The growing list of measures advocated and devised is indicative of the unsatisfactory state of the present therapeutic approach. Kenwell & Wels (121) advocate the use of human serum albumin intravenously, especially for its antitryptic activity. In 11 consecutive cases treated with 300 to 500 ml. daily for three to five days, the course of the disease was considered more benign, and hospitalization shorter, than in previous control cases. Dale (122) has employed splanchnic block for the acute episode using either multiple, bilateral paravertebral block, or single retroperitoneal left splanchnic block. Of eight patients so treated, pain was relieved completely in three and partially in five; one death occurred after each type of block. It is difficult to decide whether these types of therapy are useful additions to the usual supportive measures. Surgical therapy of chronic pancreatitis is similarly unsatisfactory. Jones & Smith (123) advocate a sphincteroplasty by excision of a wedge-shaped portion of the common bile duct, duodenal wall, and sphincteric muscle; the common duct is sutured to the duodenum. Partington (124) performed a Roux-type of jejunal anastomosis to the gall bladder or common bile duct in seven patients with chronic relapsing pancreatitis. These operations assume that chronic relapsing pancreatitis results from acute pancreatitis and that the primary defect is an increase in intraductal pressure with or without a common duct channel for biliary reflux. This may be true, but unequivocal evidence of it is not available.

CARCINOMA OF THE PANCREAS

There has been little added to the problem of carcinoma of the pancreas during the last year. The review of 125 cases by Clifton (125) illustrates the usual results of surgical therapy. Of these subjects, 19 had palliative operations with a high operative mortality (58 per cent) and very short survival ($3\frac{1}{2}$ months, average). Twelve had pancreaticoduodenectomy, with $33\frac{1}{2}$ per cent operative mortality; there was one survival over 6 years, one over 15 months, and one over 6 months. The author comments that the results of treatment in this series do not confirm the pessimistic opinion commonly held, yet they do not encourage much optimism either.

PANCREATIC EXOCRINE FUNCTION TESTS

Although the pancreas is not directly accessible, quantitative tests of its functional activity and capacity are among the best of all such procedures for the digestive tract. These tests have recently been reviewed by several authors (12, 126). The secretin test rests on well-established physiological statistical norms, and it is therefore especially unfortunate that secretin may become commercially unavailable in the United States. The difficulty of duodenal intubation required for this test remains its chief drawback, and recent years have witnessed considerable effort devoted to developing a test based on serum enzyme activity following pancreatic stimulation. None of the procedures so far reviewed is wholly satisfactory. Although the determination of serum amylase concentration remains one of the most important laboratory aids in the diagnosis of acute pancreatitis, several factors may modify its value, and these must be taken into account in evaluating any amylase determination. Because of earlier reports that sphincter spasm induced by morphine or codeine may elevate blood amylase, Pfeffer *et al.* (127) and Wapshaw (128) studied the effects of these compounds. The former found that neither morphine, meperidine (Demerol), nor codeine elevated the serum amylase values in the normal individual unless the pancreas was stimulated by a meal, the maximum response occurring within the first 4 hr. following eating. On the other hand, Wapshaw found an elevation of both lipase and amylase levels after morphine in 39 per cent of cases. Eating a meal increased the values over fasting levels, and the combination of a meal with a parasympathomimetic drug was most effective.

Chinn *et al.* (129) have varied the balance technique for the study of protein digestion and absorption, by feeding patients a meal of I^{131}-labeled protein, and measuring fecal and urinary I^{131} 72 hr. later. Comparing 5 patients with pancreatic insufficiency and 11 without, they found the difference between the two groups to be more striking in regard to fecal excretion of I^{131} than urinary excretion. The fecal excretion in the pancreatic-deficient patients was strikingly higher than in the normal groups. The test obviously depends on both pancreatic digestion and intestinal absorption, and its value remains to be established.

One of the earliest problems raised by the widespread use of vagotomy

was its effect on pancreatic function. It is clearly established that, following a complete vagotomy, insulin hypoglycemia elicits no pancreatic secretion; whether the response to secretin is affected is still under dispute. Pfeffer *et al.* (130) noticed that patients having a vagotomy had a significant reduction in volume, and amylase and bicarbonate content, of pancreatic juice as compared to a control group. The stimulus was secretin, with or without insulin. Bilateral thoracolumbar sympathectomy was without effect. This is not in keeping with previous reports and the recent studies of Routley *et al* (131), in both of which vagotomy was found to have no effect on secretin-stimulated secretion.

LITERATURE CITED

1. Palmer, E. D., *The Esophagus and its Diseases* (Paul B. Hoeber, Inc., New York, N. Y., 553 pp., 1952)
2. Lerche, W., *The Esophagus and Pharynx in Action* (Charles C Thomas, Publisher, Springfield, Ill., 229 pp., 1950)
3. Code, C. F., Hightower, N. C., Jr., and Morlock, C. G., *Am. J. Med.*, **13,** 328 (1952)
4. Wulff, H. B., and Malm, A., *Acta Chir. Scand.*, **103,** 445 (1952)
5. Gertz, T. C., *Acta Chir. Scand.*, **103,** 459 (1952)
6. Andersen, H. A., Holman, C. B., and Olsen, A. M., *J. Am. Med. Assoc.*, **151,** 608 (1953)
7. Reynolds, T. B., Freedman, T., and Winsor, W., *Am. J. Med. Sci.*, **224,** 500 (1952)
8. Linton, R. R., *Gastroenterology*, **24,** 1 (1953)
9. Palmer, E. D., Sborov, V. M., and Jahnke, E. J., Jr., *Gastroenterology*, **24,** 10 (1953)
10. Quigley, J. P., and Brody, D. A., *Am. J. Med.*, **13,** 73 (1952)
11. Hollander, F., *Am. J. Med.*, **13,** 453 (1952)
12. Janowitz, H. D., *Am. J. Med.*, **13,** 465 (1952)
13. Sweet, R. H., *J. Am. Med. Assoc.*, **151,** 376 (1953)
14. Feldman, M., Morrison, S., and Myers, P., *Gasteroenterology*, **22,** 80 (1952)
15. Melamed, A., Haukohl, R. S., and Marck, A., *Gastroenterology*, **23,** 620 (1953)
16. Rappaport, E. M., Rappaport, E. O., and Alper, A., *J. Am. Med. Assoc.*, **150,** 182 (1952)
17. Kirsner, J. B., and Palmer, W. L., *Am. J. Med.*, **13,** 615 (1952)
18. Cox, A. J., Jr., *Arch. Pathol.*, **54,** 407 (1952)
19. Cambel, P., and Sgouris, J. T., *Am. J. Pathol.*, **28,** 1079 (1952)
20. Feldman, M., *Gastroenterology*, **23,** 304 (1953)
21. Dragstedt, L. R., Oberhelman, H. A., Jr., Zubiran, J. M., and Woodward, E. R., *Gastroenterology*, **24,** 71 (1953)
22. Kirsner, J. B., *Bull. N. Y. Acad. Med.*, **29,** 477 (1953)
23. Clark, D. H., *Brit. Med. J.*, **I,** 1254 (1953)
24. Eastcott, H. H. G., Fawcett, J. K., and Rob, C. G., *Lancet*, **I,** 1068 (1953)
25. Hirschowitz, B. I., *Lancet*, **I,** 66 (1953)
26. Mirsky, I. A., Futterman, P., Kaplan, S., and Broh-Kahn, R. H., *J. Lab. Clin. Med.*, **40,** 17 (1952)
27. Mirsky, I. A., Futterman, P., and Kaplan, S., *J. Lab. Clin. Med.*, **40,** 188 (1952)
28. Martin, W. S., and Morton, W. S., *Arch. Surg.*, **65,** 382 (1952)

29. Kirsner, J. B., and Palmer, W. L., *J. Am. Med. Assoc.*, **151**, 798 (1953)
30. Rowen, B. R., Bachrach, W. H., Halsted, J. A., and Schapiro, H., *Gastroenterology*, **24**, 86 (1953)
31. Bayer, A. E., Plummer, K., and Bradford, S., *Gastroenterology*, **22**, 112 (1952)
32. Liebowitz, D., Raisin, A., Berry, C., and Roth, H. P., *J. Am. Med. Assoc.*, **150**, 672 (1952)
33. Texter, E. C., Jr., Baylin, G. J., Legerton, C. W., Jr., and Ruffin, J. M., *Am. J. Med. Sci.*, **224**, 612 (1952)
34. Rauch, R. R., and Bieter, R. N., *Surgery*, **33**, 21 (1953)
35. Palmer, W. L., Vansteenhuyse, F., and Kirsner, J. B., *Am. J. Med. Sci.*, **224**, 603 (1952)
36. Hightower, N. C., Jr., and Gambill, E. E., *Gastroenterology*, **23**, 244 (1953)
37. Ruffin, J. M., Baylin, G. J., Legerton, C. W., Jr., and Texter, E. C., Jr., *Gastroenterology*, **23**, 252 (1953)
38. Becker, D. L., Baggenstoss, A. H., and Weir, J. F., *Am. J. Clin. Pathol.*, **22**, 843 (1952)
39. Wermer, P., Kuschner, M., and Riley, E. A., *Am. J. Med.*, **14**, 108 (1953)
40. Jordan, S. M., Ruffin, J. M., Aaron, A. H., Hollander, F., Walters, W., Moore, F. D., Winkelstein, A., Thomas, J. E., Brooks, F. P., and Lorge, I., *Gastroenterology*, **22**, 297 (1952)
41. Jordan, S. M., Ruffin, J. M., Aaron, A. H., Hollander, F., Walters, W., Moore, F. D., Winkelstein, A., Thomas, J. E., Brooks, F. P., and Lorge, I., *Gastroenterology*, **24**, 280 (1953)
42. Druckerman, L. J., Weinstein, V. A., Klingenstein, P., and Colp, R., *J. Am. Med. Assoc.*, **151**, 1266 (1953)
43. Pontes, J. F., and Neves, D. P., *Gastroenterology*, **23**, 431 (1953)
44. Glazebrook, A. J., and Welbourn, R. B., *Brit. J. Surg.*, **40**, 111 (1952)
45. Everson, T. C., *Surg. Gynecol. Obstet.*, **95**, 209 (1952)
46. Welbourn, R. B., Hallenbeck, G. A., and Bollman, J. L., *Gastroenterology*, **23**, 441 (1953)
47. Chalmers, T. C., Zamcheck, N., Curtins, G. W., and White, F. W., *Am. J. Clin. Pathol.*, **22**, 634 (1952)
48. Zamcheck, N., Cotter, T. P., Hershorn, S. E., Chalmers, T. C., Ritvo, M., and White, F. W., *Am. J. Med.*, **13**, 713 (1952)
49. Crohn, B. B., *J. Am. Med. Assoc.*, **151**, 625 (1953)
50. Ogilvie, A. G., Cardoe, N., and Bentley, F. H., *Brit. Med. J.*, **II**, 304 (1952)
51. Breidenbach, L., Saltz, N. J., and Soroff, H., *Am. J. Surg.*, **85**, 18 (1953)
52. Cooper, D. R., and Ferguson, L. K., *J. Am. Med. Assoc.*, **151**, 879 (1953)
53. Caswell, H. T., Burnett, W. E., and Rosemond, G. P., *Am. J. Surg.*, **84**, 42 (1952)
54. Rogers, T. M., *J. Am. Med. Assoc.*, **150**, 473 (1952)
55. Peacock, P. R., Beck, S., and Chalmers, J. G., *J. Natl. Cancer Inst.*, **13**, 931 (1953)
56. Kobernick, S. D., Toovey, E. W., and Webster, D. R., *J. Natl. Cancer Inst.*, **13**, 979 (1953)
57. Hollander, F., *J. Natl. Cancer Inst.*, **13**, 989 (1953)
58. Komarov, S. A., *J. Natl. Cancer Inst.*, **13**, 1007 (1953)
59. Glass, G. B. J., *J. Natl. Cancer Inst.*, **13**, 1013 (1953)
60. Wolf, S., Glass, G. B. J., McNeer, G., and Bowden, L., *J. Natl. Cancer Inst.*, **13**, 1025 (1953)

61. Gardner, E. J., Woolf, C. M., and Shaffer, J. O., *J. Natl. Cancer Inst.*, **13**, 1089 (1953)

62. Horn, R. C., Jr., and Ravdin, I. S., *J. Natl. Cancer Inst.*, **13**, 1049 (1953)

63. Brown, C. H., Fisher, E. R., and Hazard, J. B., *Gastroenterology*, **22**, 103 (1952)

64. Berkson, J., and Comfort, M., *J. Natl. Cancer Inst.*, **13**, 1087 (1953)

65. Segal, H. L., Miller, L. L., and Morton, J. J., *J. Natl. Cancer Inst.*, **13**, 1079 (1953)

66. Flood, C. A., Jones, B., Rotton, W. M., and Schwarz, H., *Gastroenterology*, **23**, 607 (1953)

67. Malach, M., and Banks, B. M., *New Engl. J. Med.*, **247**, 880 (1952)

68. Wigh, R., and Swenson, P. C., *J. Natl. Cancer Inst.*, **13**, 1075 (1953)

69. Sloan, R. D., Morgan, R. H., and Wolfson, J. J., *J. Natl. Cancer Inst.*, **13**, 1067 (1953)

70. Cooper, W. A., and Papanicolaou, G. N., *J. Am. Med. Assoc.*, **151**, 10 (1953)

71. Traut, H. F., Rosenthal, M., Harrison, J. T., Farber, S. M., and Grimes, O. F., *Surg. Gynecol. Obstet.*, **95**, 709 (1952)

72. Ochsner, A., and Blalock, J., *J. Am. Med. Assoc.*, **151**, 1377 (1953)

73. Wangensteen, O. H., *J. Natl. Cancer Inst.*, **13**, 981 (1953)

74. Landboe-Christensen, E., Berk, L., and Castle, W. B., *Am. J. Med. Sci.*, **224**, 1 (1952)

75. Glass, G. B. J., *Gastroenterology*, **23**, 219 (1953)

76. Chapman, W. P., Wyman, S. M., Mora, L. O., Gillis, M. A., and Jones, C. M., *Gastroenterology*, **23**, 234 (1953)

77. Cummins, A. J., *J. Clin. Invest.*, **31**, 928 (1952)

78. Taylor, R. M., and Wightman, K. J. R., *Am. J. Med. Sci.*, **224**, 190 (1952)

78a. Warren, S., and Sommers, S. C., *Program of the Scientific Assembly, 102nd Annual Meeting*, p. 153 (Am. Med. Assoc., New York, N. Y., June, 1953)

79. Martin, F. R. R., and Carr, R. J., *Brit. Med. J.*, **I**, 700 (1953)

80. Storrs, R. C., and Hoekelman, R. A., *New Engl. J. Med.*, **248**, 320 (1953)

81. Grace, W. J., *Gastroenterology*, **23**, 542 (1953)

82. Sauer, W. G., Brown, P. W., and Dearing, W. H., *Gastroenterology*, **22**, 550 (1952)

83. Comfort, M. W., Wollaeger, E. E., Taylor, A. B., and Power, M. H., *Gastroenterology*, **23**, 155 (1953)

84. Cummins, A. J., and Almy, T. P., *Gastroenterology*, **23**, 179 (1953)

85. Rivas, F. D., Morales, F. H., and Koppisch, E., *J. Am. Med. Assoc.*, **150**, 647 (1952)

86. Upton, A. C., *Am. J. Clin. Pathol.*, **22**, 755 (1952)

87. Jackson, W. P. U., and Linder, G. C., *S. African J. Clin. Sci.*, **2**, 70 (1951)

88. Clatworthy, H. W., Jr., Saleeby, R., and Lovingood, C., *Surgery*, **32**, 341 (1952)

89. Kozoll, D. D., Pobanz, D. M., and Baker, L., *Gastroenterology*, **23**, 578 (1953)

90. Spencer, H., Lewin, I., and Laszlo, D., *Am. J. Med.*, **14**, 636 (1953)

91. Kamijo, K., Hiatt, R. B., and Koelle, G. B., *Gastroenterology*, **24**, 173 (1953)

92. Machella, T. E., *Am. J. Med.*, **13**, 760 (1952)

93. Hiatt, R. B., Engle, C., Flood, C., and Karush, A., *J. Clin. Invest.*, **31**, 721 (1952)

94. Brown, G. M., and Mc Auley, J. S., *J. Am. Med. Assoc.*, **150**, 1587 (1952)

95. Tulin, M., Kern, F., Jr., and Almy, T. P., *J. Am. Med. Assoc.*, **150**, 559 (1952)

96. Morrison, L. M., *J. Am. Med. Assoc.*, **151**, 366 (1953)

97. Crile, G., Jr., *Gastroenterology*, **23**, 533 (1953)

98. Uyeyama, K., Giansiracusa, J. E., Althausen, T. L., and Harper, H. A., *Gastroenterology*, **23**, 143 (1953)

99. Kleckner, M. S., Jr., Stauffer, M. H., Bargen, J. A., and Dockerty, M. B., *Gastroenterology*, **22**, 13 (1952)

100. Kallet, H. I., *Am. J. Surg.*, **84**, 574 (1952)

101. Radke, R. A., *Gastroenterology*, **21**, 525 (1952)

102. Steigmann, F., Shlaes, W. H., Mintzer, S., and Schaefer, G., *Gastroenterology*, **23**, 70 (1953)

103. Buchman, E., Kullman, H. J., and Margonis, G. F., *Gastroenterology*, **21**, 391 (1952)

104. Martin, G. A., Garfinkel, B. T., Brooke, M. M., Weinstein, P. P., and Frye, W. W., *J. Am. Med. Assoc.*, **151**, 1055 (1953)

105. Vegas, J. S., *J. Am. Med. Assoc.*, **151**, 1059 (1953)

106. White, R. R., *Southern Med. J.*, **45**, 481 (1952)

107. Welch, C. E., McKittrick, J. B., and Behringer, G., *New Engl. J. Med.*, **247**, 959 (1952)

108. Cole, W. H., *Arch. Surg.*, **65**, 264 (1952)

109. Dearing, W. H., Heilman, F. R., and Sauer, W. G., *Abstracts Am. Gastroenterological Assoc. 54th Meeting*, p. 39 (Atlantic City, N. J., May, 1953)

110. Reiner, L., Schlesinger, M. J., and Miller, G. M., *Arch. Pathol.*, **54**, 39 (1952)

111. Spencer, F. M., *Gastroenterology*, **21**, 535 (1952)

112. Whitehouse, W. M., and Martin, O., *Radiology*, **60**, 215 (1953)

113. Dunne, E. F., Jensen, E. H., and Hughes, C. R., *Radiology*, **60**, 210 (1953)

114. Christensen, F., Dam, H., and Prange, I., *Acta Physiol. Scand.*, **27**, 315 (1953)

115. Dixon, C. F., and Owen, H. W., *Surg. Clin. North America*, 1177 (1952)

116. Howard, M. A., *Am. J. Surg.*, **84**, 408 (1952)

117. Branch, C. D., *Surg. Gynecol. Obstet.*, **97**, 246 (1953)

118. Cole, W. H., *J. Am. Med. Assoc.*, **150**, 631 (1952)

119. Darling, R. C., DiSant'Agnese, P. A., Perera, G. A., and Andersen, D. H., *Am. J. Med. Sci.*, **225**, 67 (1953)

120. Brooks, F. P., and Thomas, J. E., *Gastroenterology*, **23**, 36 (1953)

121. Kenwell, H. N., and Wels, P. B., *Surg. Gynecol. Obstet.*, **96**, 169 (1953)

122. Dale, W. A., *Surgery*, **32**, 605 (1952)

123. Jones, S. A., and Smith, L. L., *Ann. Surg.*, **136**, 937 (1952)

124. Partington, P. F., *Arch. Surg.*, **65**, 532 (1952)

125. Clifton, E. E., *Arch. Surg.*, **65**, 290 (1952)

126. Dreiling, D. A., *N. Y. State J. Med.*, **53**, 671 (1953)

127. Pfeffer, R. B., Stephenson, H. E., Jr., and Hinton, J. W., *Gastroenterology*, **23**, 482 (1953)

128. Wapshaw, H., *Brit. Med. J.*, **I**, 373 (1953)

129. Chinn, A. B., Lavik, P. S., Stitt, R. M., and Buckaloo, G. W., *New Engl. J. Med.*, **247**, 877 (1952)

130. Pfeffer, R. B., Stephenson, H. E., Jr., and Hinton, J. W., *Ann. Surg.*, **136**, 585 (1952)

131. Routley, E. F., Mann, F. C., Bollman, J. L., and Grindlay, J. H., *Surg. Gynecol. Obstet.*, **95**, 529 (1952)

DISEASES OF THE CARDIOVASCULAR SYSTEM[1]

By J. Gibson Graham and R. D. H. Maxwell

The Royal Alexandra Infirmary, Paisley, Scotland

Coronary Arterial Disease

Exogenous cholesterol metabolism in man has been studied by Biggs *et al.* (1) using tritium-labeled cholesterol. Ingested cholesterol was demonstrated in an atherosclerotic aorta. Severe hypercholesterolemia was produced in rats by Page & Brown (2), intimal lipid infiltration occurring but atherosclerosis failed to develop. A sustained low blood cholesterol level has been obtained in man by Pollak (3) using sitosterol in oral dosage of 5 to 10 gm. per day. Paterson (4) considers the precipitating factor in coronary artery occlusion of capillary rupture within the atherosclerotic plaques is more important than the degree of atherosclerosis.

The early assessment of coronary artery insufficiency is of importance. Master *et al.* (5) give criteria of electrocardiographic changes following their exercise test which they consider to be more significant than the resting electrocardiogram. Ischemic electrocardiographic changes comparable with those following exercise have been demonstrated by Contro *et al.* (6) after amyl nitrite inhalation, and the use of this as a simple functional test is suggested.

Attention has been drawn by Papp & Smith (7) to the clinical entity of slight cardiac infarction. Cardiac pain, angina of effort, and a variable degree of shock and failure occur, but laboratory and clinical signs are minimal. The pathological lesions correspond to small areas of infarction which represent the acute stage of patchy myocardial sclerosis resulting from arteriosclerotic narrowing of the main coronary arteries and not from a local arterial occlusion. Clinical recovery occurs in a high proportion of these cases. Q waves were absent in one-half of this group of patients and R-T changes were of the subacute type. Changes were found mainly in leads III R and aVFr, exercise being useful in demonstrating ischemia. Severe cases of posterior infarction had a mortality of 33 per cent; the prognosis in the moderate group was good. Elek *et al.* (8) have found the left back leads of value in diagnosis.

High posterolateral infarction of the anatomical left surface of the heart has been the subject of an interesting study by Tulloch (9). Diagnostic signs of infarction are found in VL and lead 1. A predominant R wave is found in V1, with absence of a definite transitional zone in the precordial leads, a high upright T wave in two or more of these, and in the acute stage, S-T depression. Additional back leads are useful.

Electrocardiographic and pathologic changes following infarction of the

[1] The survey of literature pertaining to this review covers the period from July. 1952 to June, 1953.

51

interventricular septum have been correlated by Osher & Wolff (10). Septal lesions were always associated with infarction of the free wall anteriorly or posteriorly, both walls being usually involved. Massive septal infarction is probably usually fatal, but septal involvement of significant degree is common in myocardial infarction. A diagnosis of septal infarction can be made when conduction defects appear during the course of acute myocardial infarction, and in their absence the appearance of QS deflections with abnormally elevated S-T segments in right precordial leads is strongly suggestive of septal involvement.

Methods of diagnosis of myocardial infarction in the presence of anomalous conduction have been suggested by Wolff & Richman (11).

Brigden & Shillingford (12) in their examination of vectorcardiograms have found constant deviation of the loop from the site of infarction which is demonstrated best in the horizontal plane in anterior, and the frontal plane in posterior infarctions. The ballistocardiogram was found to be more sensitive than the electrocardiogram by Scarborough *et al.* (13) in the detection of coronary artery insufficiency, but its diagnostic significance was impaired by the frequency of ballistic abnormality in normal subjects, which increases with age. It is suggested that significance be attached to abnormal ballistocardiograms from subjects under the age of 50 and to normal ballistocardiograms from those over the age of 60.

The mortality rate of patients with shock following myocardial infarction was found by Selzer (14) to be more than twice that of patients without shock. Four categories were evident: immediate mild shock, immediate fatal shock, delayed shocklike state associated with arrhythmias, and delayed shocklike state with fatal cardiac failure. It is suggested that early shock may be initiated by a vasomotor mechanism, but the last group is a result of irreversible cardiac failure of the forward type. Selzer (15), using dogs, has described a method by which the competence of the heart can be estimated by response of the intraventricular pressure to a standardized stimulus overloading the left ventricle by increasing the peripheral resistance. It was necessary to ligate two major branches of the coronary artery thereby producing a massive myocardial infarction before cardiogenic shock was reproduced.

The necessity for immediate and vigorous treatment of shock following acute myocardial infarction is emphasised by Goodnick & Knox (16), who record improvement in survival following treatment with vasopressor drugs and blood or plasma. An untreated mortality of 80 per cent was the experience of Hellerstein *et al.* (17) who have found mephentermine produced a satisfactory pressor response which did not produce or aggravate congestive failure.

An extensive review of the mechanisms involved in blood clotting has been prepared by Wright (18) together with a survey of the methods of preventing or protracting this. Attention is drawn to the complexity of the process, its unpredictability, and lack of a certain relationship between the clotting time of the sample of peripheral venous blood withdrawn and the

clotting time elsewhere in circulation. A new factor, serum accelerator-globulin, is mentioned, and its physico-chemical involvement is examined. It is suggested that heparin and other anticoagulants, by increasing the negative zeta potential of the vessel wall, inhibit initial clotting stages by increasing a tendency to repel blood components with possible lessening of the platelet adhesiveness. Blood stasis with sludging is an important feature in patients confined to bed. Of the anticoagulants used, ethyl biscoumacetate (Tromexan) remains the most useful. Rosenthal & Weaver (19) have found that the heparin clotting time, which provides an indication of over-all coagulability, was accelerated in 74 per cent of patients with acute myocardial infarction examined within three weeks after the attack. Peel (20) has used Rosenthal's heparin-retarded coagulation time as a method of selection of patients with coronary artery disease for anticoagulant therapy, suggesting that thereby it can be concentrated upon those patients most in need of it.

Further experience has mainly confirmed the value of anticoagulants in myocardial infarction. Loudon et al. (21) have recorded a mortality of 41 per cent in the control group and 25 per cent in the treated group. Griffith et al. (22) experienced a significant reduction in thromboembolic complications. Scarbrone et al. (23) have confirmed the general advantages of anticoagulant therapy. The employment of anticoagulants is considered by Gilchrist (24) to be an outstanding contribution to the treatment of myocardial infarction, and he states that by their efficient use the death rate over the first six weeks can be halved and the dangers of thromboembolic complications be reduced to negligible proportions while they have in addition a favourable influence on the outcome of the shock syndrome. The need for prompt reversal of the shock mechanism and the methods available have been noted. However, Feldman et al. (25) found that anticoagulant therapy had no influence upon the mortality of their series of patients. Further to this, Schnur (26) has critically examined the progress of 1350 patients with acute myocardial infarction admitted over a 10 year period, and he has surveyed the literature critically. He states unequivocally that there is no convincing evidence of the value of anticoagulant therapy and considers that there is no indication for such treatment as a routine, but the theoretical advantages may justify the use of anticoagulant drugs in the more seriously ill patient.

The early complications of cardiac infarction have been studied by Pearson (27) who has commented on the dangers not only from the local effects of the lesion and the circulatory depression which follows, but also from the immobility which must be imposed by the physician, together with the hazards that may attend more active treatment. The length of survival after myocardial infarction has been examined by Smith (28) who has confirmed the absence of relationship between the severity of the attack and the subsequent length of life. A longer survival time was found for women than for men in those who live into the second decade, when hypertension becomes a

more important factor in shortening the survival period. The possible mechanisms capable of augmenting or replacing the normal coronary supply following occlusive atherosclerosis have been stated by Bailey *et al.* (29) to be the development of additional vascularity at the base of the heart and in pericardial adhesions, over-development of normal intracardiac openings, and enlargement of intercoronary vascular communications.

Experimental work by Hahn *et al.* (30) suggests that satisfactory retrograde circulation through the capillary bed can be obtained by arterialisation of the coronary sinus. However, Eckstein *et al.* (31) have demonstrated that arterialisation of the coronary sinus results in a retrograde flow capable of producing only a quarter or less of the myocardial oxygen requirement. If the coronary flow is normal or reduced, myocardial anoxia results from restriction in capillary outflow. Cardio-pericardiopexy using magnesium silicate as a pericardial irritant has been performed by Thompson & Plachta (32) upon 57 patients with coronary artery thrombosis during the last 13 years, the subsequent average life duration being 5 years. Dack & Gorelik (33) basing their opinion upon three years experience with 36 patients have confirmed their opinion that this may be a useful procedure.

The prognosis of angina pectoris has been studied by Block *et al.* (34) in a large series of patients. The average age at diagnosis was 58.8 years, and the ratio of males to females was approximately 4 to 1. The mortality was greatest (15 per cent) in the first year and was approximately 9 per cent per year subsequently. Electrocardiographic abnormality was a good indication of prognosis. Obesity was found to favour survival.

Dioxyline phosphate has been found of possible value in the treatment of angina by Scott *et al.* (35). Talley *et al.* (36) considered that pentaerythritol tetranitrate was of dubious value. Binder *et al.* (37) and Port *et al.* (38) have found heparin ineffective.

VALVULAR DISEASE OF THE HEART

The prime importance of clinical signs in the differentiation of predominant mitral stenosis from predominant mitral incompetence is stressed by Logan & Turner (39) in the selection of patients for operative treatment for mitral valve disease. The quality of the first heart sound and the opening snap are diagnostic, the apical systolic murmur and atrial systolic expansion being of relatively little value. While the assessment is primarily clinical, radiography is indispensable, electrocardiography is sometimes useful in confirmation, and cardiac catheterisation is of value in difficult cases. In surveying the results of operation, it was found that a good improvement was obtained in 66 of 74 patients. Ligation of the inferior vena cava is suggested as a useful prevalvulotomy procedure in the presence of intractible edema. Wade *et al.* (40) have examined thoroughly the hemodynamic bases of the symptoms and signs in mitral valvular disease using a group of 49 patients. An inverse relation between exercise tolerance and the pulmonary arterial and capillary pressures was found, the cardiopulmonary blood volume being related directly to the pulmonary capillary pressures. Ventricularisa-

tion of the pulmonary capillary pressure curve indicated mitral incompetence and in the severer grades was associated with an apical systolic murmur although other classical signs might be absent. The degree of left auricular enlargement was greatest in the presence of auricular fibrillation, not being closely related to the height of the pulmonary capillary venous pressure. Vertical or semivertical electrical axes were almost invariably found; electrocardiographic signs of right ventricular enlargement were uncommon. Broad and bifid P waves were associated with left auricular hypertrophy. In the quantitative assessment of disability in mitral stenosis, estimation of the degree of the dominant symptom, dyspnoea, is complicated by psychological factors, and Stock & Kennedy (41) have provided a quantitative index based upon physiological change in ventilatory function during exercise. The opening snap was examined in a clinical and phonocardiographic study by Mounsey (42) who found it a useful diagnostic sign in the absence of other signs of mitral stenosis upon casual examination. It is suggested that its presence should lead to careful auscultation for the latent middiastolic murmur. Janton et al. (43) have analysed the results obtained by commissurotomy of a series of 100 consecutive cases of mitral stenosis. Functional improvement occurred in 78 patients, 9 were unimproved, 11 deaths were attributable to surgery, and 2 died during the three year follow-up from intercurrent infection. The methods of selection of patients for operation are reviewed in detail, and they correspond closely to the criteria concisely defined by Wood (44). Ravin et al. (45) have carefully examined the criteria for diagnosis of tight mitral stenosis. They note that although commisurotomy of the mitral valve has been so far limited to those suffering from this condition with a minimum of complication by other valvular involvement, it is possible to anticipate rectification of mitral stenotic pathology in patients who may suffer from other valvular lesions in view of the low mortality and good functional results. The fatalities reported by Goodwin (46) and Sancetta et al. (47) as a result of subendocardial trauma endorse the necessity to reserve cardiac catheterisation for those patients only where real difficulty of assessment exists.

Mitral incompetence has been studied by Brigden & Leatham (48). Its natural history is longer and more benign than that of mitral stenosis, but bacterial endocarditis is a more frequent complication. A difference in etiology or response to rheumatic disease is suggested. A complaint of palpitation attributable to multiple ventricular extra systoles is fairly common, but significant symptoms are few unless failure develops. The clinical signs consist of a loud apical murmur always filling systole and often maximal in late systole, extending up to and usually embracing the second sound with wide splitting of the second sound in some cases. The length of the systolic murmur, its position in systole, and relationship to the sounds are as important as loudness in differential diagnosis from aortic stenosis and associated mitral stenosis. Systolic expansion of the left auricle is the most important radiological sign.

The problem of the diagnosis of mitral incompetence accompanying

mitral stenosis has been reviewed by Logan (49) who emphasises the difficulty involved and doubts the value of systolic expansion of the left atrium as a sign of mitral incompetence. This problem of differentiation of the predominant lesion has met also with the attention of Venner & Holling (50). The frequent impossibility of preoperative differential diagnosis by all the means at present available is stated. Regurgitation may be small in volume in comparison with the volume of the left atrium and pulmonary veins and may be found only at operation. The esophageal piezocardiogram has been used by Lasser *et al.* (51) to record left atrial pressure curves, and proved to be a method of obtaining pressure patterns with a minimum of experimental complication. Soloff *et al.* (52) have prepared border electrokymograms of the cardiovascular silhouette to determine the importance of atrial border motion in differentiating organic from functional apical systolic murmurs. Plateau curves previously considered to be pathognomonic of organic mitral regurgitation were observed to occur also in normal subjects.

Rheumatic activity was found to be present in spite of negative clinical and laboratory findings in biopsy specimens from left auricular appendages resected at operations for mitral stenosis by Biorck *et al.* (53), indicating the necessity for long term observation to determine the importance of active rheumatic endocarditis following operation. Enticknap (54) does not consider that the lesions resembling Aschoff bodies necessarily indicate an acute rheumatic process. Gilroy *et al.* (55) have observed a striking engorgement of the pleurohilar veins during operation for mitral stenosis and at necropsy. They suggest that these veins form a decompressive mechanism in patients with pulmonary venous hypertension. A post mortem study has been made by Hall *et al.* (56) of the distribution of cerebral emboli with regard to the possibility of their prevention during operative procedures; no significant predilection for any one cerebral vessel and no disparity in distribution was found.

A survey of the results obtained by valvotomy for mitral stenosis was given in the *British Medical Journal* (57), and there was an annotation upon mitral regurgitation in the *Lancet* (58). A conservative assessment of the results obtainable by commissurotomy has been made by Werko *et al.* (59). Clinical improvement did not necessarily correlate with a return to normality of the pulmonary dynamics. It is considered that the prophylactic use of this operation is contraindicated.

CONGENITAL HEART DISEASE

In patients suffering from patent ductus arteriosus, Lewes (60) found that the mean resting pulse pressure was significantly greater than in control subjects. A fall in diastolic pressure after exercise occurred uncommonly and could not be regarded as of diagnostic significance of this lesion. McCord & Blount (61) have examined right atrial pressure curves in tricuspid regurgitation, demonstrating ventricularisation of the pressure wave. A new radioscopic sign of tricuspid atresia consisting of contraction of the posterior

cardiac border after the anterior in the left oblique position has been described by Snow (62).

Campbell & Deuchar (63) have reviewed the results of 200 anastomotic operations in patients with congenital heart disease. Excellent results followed the operative treatment of Fallot's tetralogy, 75 per cent benefited greatly against an operative mortality of 8 per cent. Less satisfactory results were obtained in the smaller number of patients who had more complex lesions; the operative indications are still to be defined.

An examination of autopsy reports upon patients with pure pulmonary stenosis has been made by Selzer & Carnes (64) who conclude that this lesion does not in itself produce cyanosis in the absence of terminal heart failure. As a component of the tetralogy of Fallot it can be regarded as compensatory, enabling the right ventricular pressure to be elevated to that of the systemic circulation, thereby permitting a right-left shunt compatible with survival. Pulmonary stenosis can be regarded as a principal factor in the production of chronic cyanosis only if there is coexisting septal patency, and its influence upon cardiac dynamics must be taken into account prior to attempts at surgical correction. A classical machinery murmur of patent ductus arteriosus may be absent in isolated cases as has been described by Bothwell *et al.* (65) if the pulmonary arterial pressure is raised to such a degree that intermittent or complete reversal of the shunt occurs.

Congenital heart disease was found to occur in 3.17 per thousand total births by McMahon *et al.* (66). A high early mortality was found, 30 to 40 per cent only surviving to 10 years of age. Associated anomalies were observed in 21 per cent of cases, there being no definite association with any single malformation. Goyette & Palmer (67) have studied post mortem 34 cases of Marfan's syndrome of arachnodactyly and cardiovascular disease. The most common lesion was cystic necrosis of the media with aneurysmal formations of the ascending aorta. Valvular lesions were uncommon and septal defects functionally insignificant although occasionally encountered.

RHEUMATIC HEART DISEASE

Experience gained during a five year period of prophylaxis of recurrences of rheumatic fever by penicillin has been described by Kohn *et al.* (68). In contrast to the use of sulphonamides, no development of resistance by Group A hemolytic streptococci was found. Penicillin is considered to be the antibiotic of choice, and it was used in oral dosage of 800,000 units per day for the first week of each month, supplemented by extra dosage during rheumatic fever seasons. Continuous prophylaxis until the age of 25 years is advocated for the rheumatic child, and the necessity for treatment of the siblings is indicated.

Hill (69) has extended the previous work upon C-reactive protein, the presence of which was a sensitive test for the degree of rheumatic activity. Changes in the concentration were found to parallel variations in the sedimentation rate (ESR), but a fall in the concentration occurred before a fall

in the latter during convalescence. The radiological diagnosis of rheumatic pericardial effusion has been studied by Besterman & Thomas (70) who found that the most consistent changes in the early stages were a sudden increase of cardiothoracic ratio and straightening of the left border. The necessity to distinguish effusions from cardiac enlargement is emphasised; cardiac catheterisation may be indicated.

A study of the gentisic acid derivatives in the treatment of rheumatic fever has been made by Clarke *et al.* (71) who claim that the gentisates are much better tolerated and are more effective than other forms of therapy. Clarke & Mosher (72) have studied the absorption and excretion of gentisic acid. Aspirin was found to be better than 3-hydroxy-phenylcinchoninic acid by Clarke & Houser (73) in the control of arthritis, fever, and raised ESR. A limited extension to the use of cortisone and ACTH has been recorded by Bach *et al.* (74) whose observations were in accord with the suggestion that salicylates exert their pharmacological activity by engendering adrenocortical excess. Golden & Hurst (75) have had the opportunity to examine the effect of treatment with cortisone upon a patient dying with acute rheumatic heart disease, finding inhibition of the inflammatory reaction without demonstrable alteration of the collagen injury.

Pericarditis

The distinguishing features of acute benign pericarditis of unknown etiology in differentiation from other forms are recorded by Davies (76). The onset is sudden with fever and a pericardial rub. Pleural and pericardial effusions often occur; recovery usually takes place in two or three months. Sawyer *et al.* (77) have investigated the effect upon the intracardiac pressure and blood flow in constrictive pericarditis. It is concluded that the effect upon the left ventricle is of prime importance; there is a rise in pulmonary venous pressure. The necessity for operative treatment is confirmed. The association of chronic constrictive pericarditis and rheumatic heart disease has been examined by Kaltman *et al.* (78) who conclude that the two conditions may coexist although they are not causally related. Sokoloff (79) has drawn attention to the incidence of pericarditis in patients suffering from rheumatoid arthritis.

Heart Disease In Pregnancy

A conservative assessment of the hazards of pregnancy in women with heart disease has been made by Bramwell (80). A classification into which patients may be grouped is given, and the view-point throughout is to substantiate the opinion that heart disease is no contraindication to pregnancy and that the risk in the past has been grossly exaggerated. The hazards in the main constitute congestive heart failure, pulmonary edema, and fibrillation. It is emphasized that surgical treatment is an unjustifiable risk in the management of a woman admitted desperately ill with a failing heart. Normal medical measures often convert a hopeless case into a reasonable surgical risk and relief of heart failure will often permit of normal delivery

which carries less risk than Caesarian section. Apart from a single exception of coarctation of the aorta pregnancy should be allowed to pursue its normal course, and interference is usually unjustified. Acute pulmonary edema requires special vigilance; congestive heart failure usually responds well to treatment if recognised early, and auricular fibrillation is not necessarily a bar to pregnancy provided adequate antenatal and postnatal care can be assured.

ELECTROCARDIOGRAPHY

Phillips *et al.* (81) have found that the electrocardiogram is the best single technique in cardiac case finding. All 12 leads should be recorded. However, 13 per cent of presumably normal individuals would be erroneously suspected of possible heart disease. A group of patients with pulmonary tuberculosis was examined by Fox *et al.* (82) to determine differentiation between abnormal electrocardiographs produced by cardiac displacement and those attributable to myocardial damage. P wave changes were found to be significant. RS-T changes occur sometimes in normal subjects, and their incidence is increased in pulmonary disease necessitating caution in interpretation. Comparison of accurately defined heart position at post mortem by Grant (83) with the ante mortem QRS axis deviation demonstrated that the criteria in unipolar electrocardiography for identifying the position and rotation of the heart have little validity. The left ventricle and interventricular septum have a remarkable constancy of position in normal and diseased subjects; significant rotation was not encountered. From further investigation of the mechanisms involved in auricular flutter and fibrillation, Scherf *et al.* (84) conclude that a differentiation continues to be justified. A theory is proposed by which fibrillation is characterised by the presence of multiple tachysystolic centers. A panoramic vectorcardiograph has been used by Milnor *et al.* (85) to resolve the conflicting theories upon the presentation of electrical activity by unipolar leads. Their observations suggest that these leads are not semi-direct and influenced principally by the myocardium underlying the exploring electrode but confirm the hypothesis that the unipolar leads depend more upon their axes in the cardiac electrical field than upon localised preferential conduction. The effect of prolonged cooling of the anterior chest wall upon precordial tracings has been studied by Brink & Goodwin (86) who have obtained results suggesting that repolarisation follows the same path as depolarisation, from within out and confirming that isolated T wave changes represent only superficial muscle damage. Lepeschkin & Surawicz (87) have suggested that confusion of an elevated U wave with the T wave may suggest a prolonged Q-T. The corrected Q-T duration in hypopotassemia without hypocalcemia is not prolonged. Palmer (88) has noted the rarity of reports upon isolated U wave negativity and considers empirical knowledge of its significance is overdue. Westlake *et al.* (89) have shown that crystalline digitalin (Digitoxin) changes the order of repolarisation in a predictable manner though in an unpredictable amount in both normal and abnormal hearts, by acceleration of repolarisation in subendocardial muscle with abolition of the normal ventricular

gradient. A practical spatial vector analyzer for the conventional electro-cardiogram has been devised by Simmonson (90).

BALLISTOCARDIOGRAPHY

Standardization of methods of preparing records and interpreting tracings has still to be accomplished. Important contributions on standardization have been made by Rappaport *et al.* (91) in their analysis of the factors which fundamentally affect ballistocardiographs, and in the subsequent study by Thompson *et al.* (92) of the normal ballistocardiogram in which the causation of the various time relationships with allowance for phase distortion is discussed. An attempt to standardize the normal tracing has also been made by Scarborough *et al.* (93) who have noted the high incidence of abnormal ballistocardiograms in the older age groups. Using the Dock electromagnetic undamped direct ballistocardiograph, Tannenbaum *et al.* (94) have shown the HIJKL complex is related entirely to the events of ventricular systole, the M, N, and O waves occurring during diastole. The Nickerson ballistocardiogram was found by Jones (95) to show increasingly frequent abnormality of I and J waves in arteriosclerotic heart failure as opposed to other forms of heart disease in the older age groups. The alterations which take place during respiration have been examined by Gubner *et al.* (96). The status of the ballistocardiogram has been discussed by Starr (97) who has pointed out that the technique enables an assessment of the strength and the weakness of the myocardium beyond that available by any other method in current use and has suggested its use in assessing the prognosis in myocardial infarction. A consistent deformity of the early systolic portion of the complex was recorded in mitral stenosis by Davis *et al.* (98) who found it was reduced by commissurotomy.

PHONOCARDIOGRAPHY

Leatham (99) has prepared a thorough appreciation of the principles, techniques, and status of this method of investigation.

HEART FAILURE

The dynamics of heart failure have been surveyed extensively by Mc-Michael (100, 101). In failure, the minute volume of the cardiac output is maintained initially at the expense of hypertrophy of the heart and later by congestion of the lungs with a rise in venous pressure which is at first compensatory but is later associated with a hypodynamic state of failure. In left ventricular failure, the output is sustained, therefore, at the expense of pulmonary hypertension. Digitalis is indicated in hypodynamic failure, and the uncertainty of action is occasioned by the relative effect upon the left and right heart. When failure is associated with mitral stensosis the unreliable response to digitalis is attributable to its inability to strengthen a fibrillating auricle or alter the mechanics of the sclerosed valve. but it produces a beneficial reduction in the heart rate. Commissurotomy is an especially welcome operation. The importance of differentiation of hypodynamic con-

gestion in which the administration of digitalis will be beneficial from compensatory states of congestion is emphasized.

Active pulmonary vasoconstriction has been suggested to occur in heart failure by Halmagyl *et al.* (102). Together with Kelley *et al.* (103) they have used vasodilators and have obtained a beneficial effect.

Procaine amide has been used intramuscularly by Enselberg & Lipkin (104) who have found it a safe and effective method for the treatment of cardiac arrhythmias. The value of this drug has been confirmed by Kelley *et al.* (105). Schwartz *et al.* (106) and Miller *et al.* (107) have indicated that procaine amide should not be used in atrioventricular dissociation, and Schwartz *et al.* (108) have found quinidine is also contraindicated. Miller *et al.* (109) and Hansen *et al.* (110) have used procaine amide or quinidine to restore sinus rhythm in patients with auricular fibrillation, and their results have indicated that this should be attempted.

Capps *et al.* (111) have stated that mercurial diuretics have no primary effect on the reabsorption of water, but the increased urine flow results secondarily from increased eliminations of ions. Lowe (112) has postulated a water volume controlling mechanism having restoring and disturbing components which may be partially blocked by mercurial diuretics. Moyer *et al.* (113) have reported satisfactory diuresis was obtained following oral dosage of the mercurial diuretic, Neohydrin, gastrointestinal intolerance limiting therapy in 10 per cent. The nonmercurial oral diuretic, 1-propyl-3-ethyl-6-aminouracil, was found active by Hellman *et al.* (114), but the incidence of toxic symptoms was too high to permit of clinical application.

Duncan (115) has shown that the sodium adsorption of exchange resins is of unabsorbed dietary origin rather than that contained in the intestinal secretion, and the amount varies with the degree of edema. Cation exchange resin has been found useful by Peel & Semple (116), but they emphasise the necessity for biochemical control during the early stages of treatment.

Peripheral Vascular Disease

The association of angina pectoris and intermittent claudication has been reviewed by McDonald (117). Using limbs amputated following arteriosclerotic gangrene, Wessler & Schlesinger (118) have been able to compare radiographic and anatomical appearances. Their results show that radiographic findings bear no relation to the presence or location of arterial occlusions. Surprisingly rich interarterial anastomoses were found, gangrene occurs only after multiple clot formation justifying the therapeutic use of anticoagulants. Examination of the clinical circumstances preceding amputation have led Wessler & Silberg (119) to believe that fresh occlusions constitute the major danger. These are controllable by anticoagulant therapy, and antibiotics will control excessive demands upon the compromised circulation from infection. Such therapy was concluded to be of greater importance than attempts to stimulate the collateral circulation. Kinmonth & Hadfield (120) have advocated preganglionic sympathetic section in preference to ganglionectomy in the treatment of Raynaud's disease. Green *et al.* (121)

and Green & Grimsley (122) have studied antiadrenergic drugs and find Regitine active in vasospasm and arteriosclerotic disease.

HYPERTENSIVE HEART DISEASE

In view of the clinical experience of improvement in obese hypertensive patients following weight reduction, Martin (123) examined the effect upon the blood pressure. Symptomatic improvement was not accompanied by any definite fall in pressure. Droller *et al.* (124) were unable to find any significant correlation between the blood pressure and the symptoms, signs, and general condition of the patient. Excellent results have been reported by Pickering & Heptinstall (125) following excision of pyelonephritic kidneys, but malignant hypertension was not improved. Unilateral renal disease may cause severe and accelerated hypertension; the importance of early recognition has been emphasised since there is a prospect of cure by nephrectomy. The blood pressure was restored to normal by nephrectomy in 20 of a series of 40 patients studied by Perera & Haelig (126).

The pathogenesis of malignant hypertension has been reviewed by Pickering (127). It is suggested that the arteriolar lesions depend only upon the level of the pressure in the artery, and that papilledema is the direct result of a severe increase in diastolic pressure. Malignant hypertension is regarded as a syndrome of albuminuric retinitis, rapidly progressive renal failure, and postmortem evidence of arteriolar necrosis. This syndrome may follow in all the conditions associated with severe hypertension should the diastolic pressure rises to high levels, usually over 140 mm. Hg, but subject to individual variations. Regression is possible if the pressure can be lowered in time. The symptomatology and clinical signs presenting in a group of 104 cases of malignant hypertension have been examined by Schottstaedt & Sokolow (128) who have found an average age of onset of 42 years. They consider that an increase in survival time is to be expected if vigorous therapy is applied before renal function is impaired and there is irreversible damage to cerebral vessels and the heart. A useful standard of course and prognosis of hypertension in the absence of specific hypotensive measures has been supplied by Leishman (129). Obesity and hypertension proved a favourable combination. He regards malignant hypertension as an accelerated form of the disease, and a benign slowly progressive hypertension is recognized as the most common form and has a good prognosis. The rapidity of development of vascular changes appear to be governed by the height of the diastolic pressure, the critical level suggested being 130 mm. Hg.

Allen (130), Morissey *et al.* (131), and D'Abreu (132) have stated that sympathectomy is of value in the treatment of hypertension, but it is acknowledged that this operation should be resorted to only in the absence of a response to medical treatment. Adrenalectomy has been advocated by Thorn *et al.* (133) and Green *et al.* (134), and subtotal adrenalectomy has been combined with sympathectomy by Wolferth *et al.* (135). The value of adrenalectomy has been disputed by Merrill (136).

Further experience with a number of drugs active in reducing the blood

pressure has been recorded. Moyer & Caplovitz (137) have confirmed the hypotensive action of Regitine but found its therapeutic use was limited by development of tolerance and by intestinal irritation precluding oral dosage. Scott *et al.* (138) found that oral administration of a mixture of dehydrogenated alkaloids of ergot (C.C.K. 179) produced a marked fall in blood pressure and improvement in hypertensive patients. The activity of protoveratrine and its suitability for clinical use have been defined by Meilman & Krayer (139). A thiophanium derivative (Ro 2-2222) has been examined by Sarnoff *et al.* (140) particularly in regard to its use in the management of acute pulmonary edema. Redisch *et al.* (141) have used a Dibenamide analogue. A further clinical examination of the effect of hexamethonium has been made by Morrison (142) who has confirmed the hypotensive activity and usefulness of this drug in the treatment of hypertension. Morrison & Paton (143) have advanced the information available upon its effect on the normal subject. New homologues of hexamethonium have been described by Maxwell & Campbell (144) which are considered to be of potential greater usefulness in the management of hypertension than the original drug. The control of hypertension has been reviewed by Platt (145) who has endorsed the value of hypotensive drugs.

LITERATURE CITED

1. Biggs, M. W., Kritchevsky, D., Colman, D., Gofman, J. W., Jones, H. B., Lindgren, F. T., Hyde, G., and Lyon, T. P. *Circulation*, **6**, 359 (1952)
2. Page, I. H., and Brown, H. B., *Circulation* **6**, 681 (1952)
3. Pollak, O. J., *Circulation*, **7**, 702 (1953)
4. Paterson, J. C., *Circulation*, **6**, 732 (1952)
5. Master, A. M., Pordy, L., Chesky, K., *J. Am. Med. Assoc.*, **151**, 458 (1953)
6. Contro, S., Haring, O. M., and Goldstein, W., *Circulation*, **6**, 250 (1952)
7. Papp, C., and Smith, K. S., *Am. Heart J.*, **44**, 696 (1952)
8. Elek, S. R., Herman, L. M., and Griffith, G. C., *Circulation*, **7**, 656 (1953)
9. Tulloch, J. A., *Brit. Heart J.*, **14**, 379 (1952)
10. Osher, H. L., and Wolff, L., *Am. Heart J.*, **45**, 429 (1953)
11. Wolff, L., and Richman, J. J., *Am. Heart J.*, **45**, 545 (1953)
12. Brigden, W., and Shillingford, J., *Brit. Heart J.*, **14**, 339 (1952)
13. Scarborough, W. R., Mason, R. E., Davis, F. W., Singewald, M. L., Baker, B. M., and Lore, S. A., *Am. Heart J.*, **44**, 645 (1952)
14. Selzer, A., *Am. Heart J.*, **44**, 1 (1952)
15. Selzer, A., *Am. Heart J.*, **44**, 12 (1952)
16. Goodnick, A., and Knox, F. H., *Circulation*, **7**, 511 (1953)
17. Hellerstein, H. K., Brofman, B. I., and Caskey, W. H., *Am. Heart J.*, **44**, 407 (1952)
18. Wright, I. S., *Circulation*, **5**, 161 (1952)
19. Rosenthal, R. L., and Weaver, J. C., *Circulation*, **6**, 257 (1952)
20. Peel, A. A. F., *Brit. Heart J.*, **15**, 8 (1953)
21. Loudon, I. S. L., Pease, J. C., and Cooke, A. M., *Brit. Med. J.*, **1**, 911 (1953)
22. Griffith, G. C., Stragnell, R., Levinson, D. C., Moore, F. J., and Ware, A. G., *Ann. Internal Med.*, **37**, 867 (1952)
23. Scarbrone, L. A., Beck, D. F., and Wright, I. S., *Circulation*, **6**, 489 (1952)
24. Gilchrist, A. R., *Brit. Med. J.*, **2**, 351 (1952)

25. Feldman, L., O'Conner, W. R., Friedman, I. A., and Fischer, J. W., *Am. Heart J.*, **44**, 112 (1952)
26. Schnur, S., *Circulation*, **7**, 855 (1953)
27. Pearson, H. E. S., *Brit. Med. J.*, **2**, 4 (1953)
28. Smith, C., *J. Am. Med. Assoc.*, **151**, 167 (1953)
29. Bailey, C. P., Ceckeler, G. D., Truex, R. C., Likoff, W., Antonius, N. A., Angulo, A. W., Redondo-Ramirez, H. P., and Neptune, W., *J. Am. Med. Assoc.*, **151**, 441 (1953)
30. Hahn, R. S., Kim, M., and Beck, C. S., *Am. Heart J.*, **44**, 772 (1952)
31. Eckstein, R. W., Hornberger, C., and Sano, T., *Circulation*, **7**, 422 (1953)
32. Thompson, S. A., and Plachta, A., *J. Am. Med. Assoc.*, **152**, 678 (1953)
33. Dack, S., and Gorelik, A. N., *Am. Heart J.*, **45**, 772 (1953)
34. Block, W. J., Crumpacker, E. L., Dry, T. J., and Gage, R. P., *J. Am. Med. Assoc.*, **150**, 259 (1952)
35. Scott, R. C., Seiwert, V. J., Fowler, N. O., and McGuire, J., *Circulation*, **6**, 125 (1952)
36. Talley, R. W., Beard, O. W., and Doherty, J. E., *Am. Heart J.*, **44**, 466 (1952)
37. Binder, M. J., Kalmanson, G. M., Drenick, E. J., and Rosove, L., *J. Am. Med. Assoc.*, **151**, 967 (1953)
38. Port, M., Katz, A., Hellman, E., and Enselberg, C. D., *Am. Heart J.*, **45**, 769 (1953)
39. Logan, A., and Turner, R., *Lancet*, **I**, 1007 (1953)
40. Wade, G., Werko, L., Eliasch, H., Gidlund, A., and Lagerlof, H., *Quart. J. Med.*, **21**, 361 (1952)
41. Stock, J. P. P., and Kennedy, M. C. S., *Lancet*, **II**, 5 (1953)
42. Mounsey, P., *Brit. Heart J.*, **15**, 135 (1953)
43. Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E., and Froio, G. F., *Circulation*, **6**, 321 (1952)
44. Wood, P., *Diseases of the Heart and Circulation*, 2nd Edition, p. 308 (Eyre and Spottiswoode, London, England)
45. Ravin, A., Slonim, N. B., Balchum, O. J., Dressler, S. H., and Grow, J. B., *J. Am. Med. Assoc.*, **149**, 1079 (1952)
46. Goodwin, J. F., *Brit. Heart J.*, **15**, 330 (1953)
47. Sancetta, S. N., Hackel, D. B., and Lynn, R. B., *Am. Heart J.*, **45**, 491 (1953)
48. Brigden, W., and Leatham, A., *Brit. Heart J.*, **15**, 55 (1953)
49. Logan, A., *Lancet*, **II**, 593 (1952)
50. Venner, A., and Holling, H. E., *Brit. Heart J.*, **15**, 205 (1953)
51. Lasser, R. P., Epstein, B., and Loewe, L., *Am. Heart J.*, **44**, 681 (1952)
52. Soloff, L. A., Zatuchni, J., and Stauffer, H. M., *Circulation*, **6**, 96 (1952)
53. Biorck, G., Winblad, S., and Wulff, H. B., *Am. Heart J.*, **44**, 325 (1952)
54. Enticknap, J. B., *Brit. Heart J.*, **15**, 37 (1953)
55. Gilroy, J. C., Marchand, P., and Wilson, V. H., *Lancet*, **II**, 957 (1952)
56. Hall, P., Dencker, S. J., and Biorck, G., *Am. Heart J.*, **44**, 600 (1952)
57. Leading Article, *Brit. Med. J.*, **1**, 1073 (1952)
58. Annotation, *Lancet*, **II**, 615 (1952)
59. Werkö, L., Biorck, G., Crafoord, C., Wulff, H., Krook, H., and Eliasch, H., *Am. Heart J.*, **45**, 477 (1953)
60. Lewes, D., *Brit. Heart J.*, **14**, 357 (1952)
61. McCord, M. C., and Blount, S. G., *Am. Heart J.*, **44**, 671 (1952)
62. Snow, P. J. D., *Brit. Heart J.*, **14**, 387 (1952)
63. Campbell, M., and Deuchar, D., *Brit. Med. J.*, **1**, 350 (1953)

64. Selzer, A., and Carnes, W. H., *Am. Heart J.*, **45**, 382 (1953)
65. Bothwell, T. H., Van Lingen, B., Whidborne, J., Kaye, J., McGregor, M., and Elliot, G. A., *Am. Heart J.*, **44**, 360 (1952)
66. McMahon, B., McKeown, T., and Record, R. G., *Brit. Heart J.*, **15**, 121 (1953)
67. Goyette, E. M., and Palmer, P. W., *Circulation*, **7**, 373 (1953)
68. Kohn, K. H., Milzer, A., and MacLean, H., *J. Am. Med. Assoc.*, **151**, 347 (1953)
69. Hill, A. G. S., *Lancet*, **II**, 558 (1952)
70. Besterman, E. M. M., and Thomas, G. T., *Brit. Heart J.*, **15**, 113 (1953)
71. Clarke, N. E., Mosher, R. E., and Clarke, C. N., *Circulation*, **7**, 247 (1953)
72. Clarke, N. E., and Mosher, R. E., *Circulation*, **7**, 337 (1953)
73. Clarke, N. E., and Houser, H. B., *Am. Heart J.*, **45**, 576 (1953)
74. Bach, F., Freedman, A., and Bernstock, L., *Brit. Med. J.*, **2**, 582 (1952)
75. Golden, A., and Hurst, J. W., *Circulation*, **7**, 218 (1953)
76. Davies, D. H., *Brit. Heart J.*, **14**, 309 (1952)
77. Sawyer, C. G., Burwell, C. S., Dexter, L., Eppinger, E. C., Goodale, W. T., Gorlin, R., Harken, D. E., and Haynes, F. W., *Am. Heart J.*, **44**, 207 (1952)
78. Kaltman, A. J., Schwedel, J. B., and Straus, B., *Am. Heart J.*, **45**, 201 (1953)
79. Sokoloff, L., *Am. Heart J.*, **45**, 635 (1953)
80. Bramwell, C., *Brit. Med. J.*, **1**, 897 (1953)
81. Phillips, E., Chapman, J. M., Goerke, L. S., *Am. Heart J.*, **45**, 319 (1953)
82. Fox, T. T., Berger, H., and Meidt, C. E., *Am. Heart J.*, **44**, 747 (1952)
83. Grant, R. P., *Circulation*, **7**, 890 (1953)
84. Scherf, D., Schaffer, A. I., and Blumenfeld, S., *Arch. Internal Med.*, **91**, 333 (1953)
85. Milnor, W. R., Talbot, S. A., and Newman, E. V., *Circulation*, **7**, 545 (1953)
86. Brink, A. J., and Goodwin, J. F., *Brit. Heart J.*, **14**, 331 (1952)
87. Lepeschkin, E., and Surawicz, B., *Circulation*, **4**, 378 (1952)
88. Palmer, J. H., *Circulation*, **7**, 205 (1953)
89. Westlake, R. E., Schiess, W. A., Arshler, L. L., and Chiu, G. G., *Am. Heart J.*, **44**, 106 (1952)
90. Simmonson, E., *Circulation*, **7**, 403 (1953)
91. Rappaport, M. B., Sprague, H. B., and Thompson, W. B., *Circulation*, **7**, 229 (1953)
92. Thompson, W. B., Rappaport, M. B., and Sprague, H. B., *Circulation*, **7**, 321 (1953)
93. Scarborough, W. R., Davis, F. W., Baker, B. M., Mason, R. E., Singewald, M. L., Lore, S. A., and Fox, L. M., *Am. Heart J.*, **45**, 161 (1953)
94. Tannenbaum, O., Schack, J. A., and Vessell, H., *Circulation*, **6**, 586 (1952)
95. Jones, R. J., *Circulation*, **6**, 389 (1952)
96. Gubner, R. S., Rodstein, M., and Ungerleider, H. E., *Circulation*, **7**, 268 (1953)
97. Starr, I., *Ann. Internal Med.*, **36**, 839 (1952)
98. Davis, F. W., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M., *Circulation*, **7**, 503 (1953)
99. Leatham, A., *Brit. Med. Bull.*, **8**, 333 (1952)
100. McMichael, J., *Brit. Med. J.*, **2**, 525 (1952)
101. McMichael, J., *Brit. Med. J.*, **2**, 578 (1952)
102. Halmagyi, D., Falkai, B., Ivanyi, J., Zsoter, T., Tenyi, M., and Szucs, Z., *Brit. Heart J.*, **15**, 15 (1953)
103. Kelley, R. T., Freis, E. D., and Higgins, T. F., *Circulation*, **7**, 169 (1953)
104. Enselberg, C. D., and Lipkin, M., *Am. Heart J.*, **44**, 781 (1952)

105. Kelley, R. T., Keegan, C. E., and Katter, G. W., *Am. Heart J.*, **44**, 851 (1952)
106. Schwartz, S. P., Hallinger, L., and Imperialli, A., *Circulation*, **6**, 193 (1952)
107. Miller, H., Nathanson, M. H., and Griffith, G. C., *Am. Heart J.*, **44**, 432 (1952)
108. Schwartz, S. P., Margolies, M. P., and Firenze, A., *Am. Heart J.*, **45**, 404 (1953)
109. Miller, G., Weinberg, S. L., and Pick, A., *Circulation*, **6**, 41 (1952)
110. Hansen, W. R., McClendon, R. L., and Kinsman, J. M., *Am. Heart J.*, **44**, 499 (1952)
111. Capps, J. N., Wiggins, W. S., Axelrod, D. R., and Pitts, R. F., *Circulation*, **6**, 82 (1952)
112. Lowe, T. E., *Lancet*, **II**, 1238 (1952)
113. Moyer, J. H., Handley, C. A., and Wilford, I., *Am. Heart J.*, **44**, 608 (1952)
114. Hellman, E., Altchek, R., Enselberg, C. D., *Am. Heart J.*, **44**, 615 (1952)
115. Duncan, L. E., *Am. Heart J.*, **45**, 802 (1953)
116. Peel, A. A. F., and Semple, T., *Brit. Heart J.*, **15**, 273 (1953)
117. McDonald, L., *Brit. Heart J.*, **15**, 101 (1953)
118. Wessler, S., and Schlesinger, M. J., *Circulation*, **7**, 641 (1953)
119. Wessler, S., and Silberg, N. R., *Circulation*, **7**, 810 (1953)
120. Kinmonth, J. B., and Hadfield, G. J., *Brit. Med. J.*, **2**, 1377 (1952)
121. Green, H. D., Gobel, W. K., Moore, M. J., and Prince, T. C., *Circulation*, **6**, 520 (1952)
122. Green, H. D., and Grimsley, W. T., *Circulation*, **7**, 487 (1953)
123. Martin, L., *Lancet*, **II**, 1051 (1952)
124. Droller, H., Pemberton, J., Roseman, C., and Grout, J. L. A., *Brit. Med. J.*, **2**, 968 (1952)
125. Pickering, G. W., and Heptinstall, R. H., *Quart. J. Med.*, **22**, 1 (1953)
126. Perera, G. A., and Haelig, A. W., *Circulation*, **4**, 549 (1952)
127. Pickering, G. W., *Circulation*, **6**, 599 (1952)
128. Schottstaedt, M. F., and Sokolow, M., *Am. Heart J.*, **45**, 331 (1953)
129. Leishman, A. W. D., *Brit. Med. J.*, **1**, 1131 (1953)
130. Allen, E. V., *Circulation*, **6**, 131 (1952)
131. Morissey, D. M., Brookes, V. S., and Cooke, W. T., *Lancet*, **I**, 403 (1953)
132. D'Abreu, F., *Lancet*, **II**, 1164 (1953)
133. Thorn, G. W., Harrison, J., Merrill, J. P., Criscitiello, M. G., Frawley, T. F., and Finkenstaedt, J. T., *Ann. Internal Med.*, **37**, 972 (1952)
134. Green, D. M., Nelson, J. N., Dodds, G. A., and Smalley, R. E., *J. Am. Med. Assoc.*, **144**, 439 (1950)
135. Wolferth, C. A., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A., and Hafkenschiel, J. H., *Ann. Internal Med.*, **35**, 8 (1951)
136. Merrill, J. P., *Ann. Internal Med.*, **37**, 966 (1952)
137. Moyer, J. H., and Caplovitz, C. C., *Am. Heart J.*, **45**, 602 (1953)
138. Scott, G. A., Buckingham, W., Brown, R. D., and Sutton, D. C., *Am. Heart J.*, **44**, 622 (1952)
139. Meilman, E., and Krayer, O., *Circulation*, **6**, 212 (1952)
140. Sarnoff, S. J., Goodale, W. T., and Sarnoff, L. C., *Circulation*, **6**, 63 (1952)
141. Redisch, W., Texter, E. C., Jr., Howard, R. M., Stillman, P. H., and Steele, J. M., *Circulation*, **6**, 352 (1952)
142. Morrison, B., *Brit. Med. J.*, **1**, 1291 (1953)
143. Morrison, B., and Paton, W. D. M., *Brit. Med. J.*, **1**, 1292 (1953)
144. Maxwell, R. D. H., and Campbell, A. J. M., *Lancet*, **I**, 455 (1953)
145. Platt, R., *Practitioner*, **169**, 325 (1952)

DISEASES OF THE KIDNEY[1]

By Elliot V. Newman and Donald G. Pocock

Vanderbilt University Hospital, Nashville, Tennessee

Introduction

This review is based on the literature from July, 1951, to August 1, 1953. This period of two years has been reviewed because the subjects selected have not previously been covered for that period.

Regulation of Water and Sodium Excretion

There has been much activity in the investigation of the mechanisms of water excretion and the factors controlling it in health and disease. One of the most important and clear cut findings is the specificity of the control of water excretion by the antidiuretic hormone of the pituitary or by injected pitressin. The specificity has been demonstrated by the separation of the effects of antidiuretic hormone (ADH) upon water from the effect on sodium excretion. This has been demonstrated both in normal subjects and subjects with edema. (1 to 4). Injections of ADH producing short term (a few hours) antidiuresis caused no change in sodium chloride excretion. Long term, continuous administration (a few days)caused secondarily large increases in sodium chloride excretion. This occurred while the serum concentrations were falling as a result of water retention. In congestive failure the daily intramuscular administration of pitressin tannate in oil caused a retention of sodium chloride (5). The retention of sodium in cardiac patients is probably attributable to the fact that the failure was worsened by the water retention. This in turn caused sodium retention. An increase in edema, dyspnea, and venous pressure will occur as a result of the water retention (6).

Some workers have suggested that the secondary dumping of salt resulting from water retention is an attempt to protect the extracellular fluid volume from overdistention. It has been suggested that there is a "volume sensitive" zone somewhere in the body which sends signals to the kidney to release sodium. This is an interesting teleological suggestion based on the idea that these are homeostatic mechanisms. The suggestion will be helpful only if it can be explained how and where there can be a center in the body with three dimensional sense, and how the stimulus is telegraphed to the kidney.

It has been pointed out that much of a natriuretic effect which was attributed to ADH may be due to variations in the solute load to the kidney, as well as to the secondary effect of overdistending the fluid compartments of the body. For example, in a patient with diabetes insipidus who developed anterior pituitary failure, the polyuria and polydypsia disappeared. When

---

[1] The survey of literature pertaining to this review was completed in September, 1953.

the solute load was increased, the symptoms reappeared (7). The inability to concentrate urine under the stimulus of a solute load is a more constant characteristic of diabetes insipidus than the volume of water intake and output, which is dependent on factors which vary the solute load (8). Leaf suggests that the inability to have a diuresis with water loading in patients with Addison's disease and in some patients with cardiac failure is probably due to abnormal continuous action of ADH (9).

Interest continues in the mechanisms which initiate and mediate the antidiuresis attributable to ADH.[2] The probable regulation of ADH secretion by variation in the serum solute concentration in normal men and dogs is again confirmed (10). Injections of hyperoncotic solutions of albumin causes antidiuresis even in a patient with Addison's disease (11). Also, it is of interest that an increased retention of salt occurred with this stimulus. Tetersdorf & Welt (12) point out, however, that the antiduiresis attributable to concentrated albumin injections may not be related to ADH. They found antidiuresis due to this stimulus was as marked in patients with diabetes insipidus. They suggest that the water retention is a passive mechanism because it includes resorption of sodium chloride. These observations emphasize that investigators must prove that a change in water output is attributable to ADH by one or both of two procedures. First, the effect of a given stimulus on salt must be separated from the effect on water excretion. Secondly, comparative control observations on patients with diabetes insipidus and on normal subjects should be made.

Other means for varying the tonicity and the volume of the extracellular fluid have been used in order to study water and also sodium excretion (4, 13, 14). Stimuli such as change in posture, sitting, standing, venous congestion, and even coitus have been used in order to gain some insight into the the mechanisms of control of water and sodium excretion (15 to 26).

In general, there is agreement that the postural stimuli of sitting and standing cause an antidiuresis and sodium retention. This occurs even when there is simultaneous salt and inert solute loading of the subject (unless the loading be done with sodium in the form of bicarbonate or phosphate which introduce more complex factors in tubular reabsorptive activity (4, 13)). In evaluating the postural stimulus, it is probably important to differentiate the passive "tilt" which may cause marked changes in circulatory dynamics from the effects of ordinary standing.

One investigator (14) finds that mild exercise increases the rate of urine secretion in men. This type of experiment must be carried out under rigidly standardized conditions. Frequently investigators will not state the conditions accurately, and in other cases it seems that factors which might signifi-

[2] The following abbreviations are used in this chapter: DOCA for desoxycorticosterone acetate; ADH for antidiuretic hormone; ACTH for adrenocorticotropin; NPN for nonprotein nitrogen.

cantly alter water and sodium excretion are not controlled. For example, a series of experiments on water and medium excretion are hardly "rigidly standardized" or "controlled" if the subjects are told to eat a "normal" breakfast in the morning of the experiment. Solute loading is important, as also may be a few cups of coffee. Smoking, eating during the experiment, and too much anxiety or emotional stimuli may alter the results.

With regard to emotion, very interesting results were obtained by Hinkle *et al.* (27). Stressful situations causing anxiety and apprehension resulted in a striking diuresis even though fluid intake had been limited for the previous twelve hours. Miles (28) reports similar results in one case. It seems that a real diuresis, not just frequency of urination can be produced by anxiety. The authors claim there was no evidence of epinephrine effect. However, it is noteworthy that administration of epinephrine may produce an increase in urine flow in dogs and rats (29, 30, 31), and norepinephrine in humans (32). The increased urine volume occurs in spite of a drop in renal blood flow and glomerular filtration rate due to medullary hormones. Some of the results with epinephrine are conflicting (31, 33). Dearborn obtained an antidiuresis with both norepinephrine and epinephrine in dogs. He makes a distinction between a variable effect immediately after injection and a long lasting antidiuresis which is attributable to ADH and can be abolished by surgical damage to the hypothalamus. There may be differences in results due to size of dose and rate of administration in studies on adrenal medullary hormones.

The role of adrenal cortical hormones in the regulation of water and sodium excretion has received attention. With stimuli such as pitressin, venous congestion, artificial expansion of extracellular fluid, and posture the patient with Addison's disease under DOCA[3] and cortisone therapy reacts like the normal (18). This suggests that variations in adrenal cortical activity are not necessary for this reaction, but the presence of an adequate supply of adrenal hormones is necessary.

On the whole, there is a strong tendency to conclude that regulation of sodium excretion under these stimuli is mediated by shifts in fluid volumes. The sensitive center has been placed in the head or the cephalad portion of the body by some workers (4, 17, 19, 34, 35, 36). On the other hand, emphasis is still being placed on the role of venous congestion, particularly in congestive failure. It would be very difficult to separate the effect of venous congestion from that of redistribution of fluid volumes. Experimental production of local venous congestion results in decreased excretion of sodium (15, 16, 37). Attempts to place the regulatory center in the cranium by manipulating cerebral venous pressure have not yielded consistent results (38). Judson *et al.* (15) found evidence to suggest that venous congestion in normal and congestive failure patients caused sodium retention when a lowered cardiac output was produced. The work of Epstein *et al.* (39) reveals marked changes in sodium excretion in patients with arteriovenous shunts

when the shunts are opened and closed. Renal circulation was not altered but there must have been large changes in cardiac output. They suggest that the stimulus changing sodium excretion arises in the arteries or veins. However, it would be very difficult to separate the local effects of opening and closing a shunt from the general shifts in blood volumes which might also be produced throughout the body. Whatever the explanation of the retention of sodium due to postural changes and venous congestion, it is apparent that rather specific and largely separate mechanisms are involved in the retention of sodium and water (40).

One of the theories of abnormal water retention is based on the idea that antidiuretic hormone may be secreted in normal amounts but is not destroyed or inactivated at a normal rate. Dochosis *et al.* (41) find a correlation of the titers of ADH in the urine with the degree of edema in patients with congestive failure and cirrhosis. White *et al.*, (42, 43) however, show that intravenous injection of pitressin to cardiac and liver disease patients causes no greater antidiuresis than in normal people. Others report similar results (44, 45).

Work by Luetscher (46) and Gordon *et al.* (47) shows a promising approach to the problems of the mechanism of sodium retention in edematous states. Using chemical fractionation and biological testing, they have found sodium retaining factors in the urine in edematous states. Chart & Shipley (48) have reported the same in cirrhosis with ascites. Demonstration of a correlation of the amount of the material in the urine with the movement of edema under cortisone or ACTH[3] therapy increases the significance of these findings (46). If a reliable, easier testing method for sodium retaining factors in serum and urine becomes available, it will undoubtedly be applied to every experimental and disease situation mentioned in this review.

Many workers have used clearance methods to determine glomerular filtration rate and effective renal plasma flow when studying water and electrolyte excretion. The presence of para amino hippuric acid (PAH) complicates the interpretation of some of the results. If the stimulus applied (e.g., epinephrine, norepinephrine, 1-hydrazinophthalazine (Apresoline), renal artery obstruction, renal vein obstruction etc.) (49, 50, 51) causes a change in renal blood flow, there will obviously be a direct, proportionate change in PAH excretion. PAH, being an acid, usually is accompanied by excretion of bases (sodium or potassium). Thus, a change in excretion of sodium and potassium cannot be interpreted solely as a direct effect of the stimulus used, but may be really just a reflection of the change in transport of para amino hippuric acid.

In acute experiments involving PAH clearance methods, adrenal medullary hormones cause a decreased sodium and potassium excretion, (49) and 1-hydrazinophthalazine an increase (51). The renal blood flows and hence the excretion of PAH must have increased also. On the other hand, Duncan *et al.* (52) have shown that chronic administration of adrenal medullary

hormones causes an increased excretion of sodium. The discrepancy between acute and chronic experiments may be explained (as is frequently the case in experimental work) by the fact that too many factors are manipulated simultaneously during an acute experiment.

There have been several studies on the mechanisms of diurnal variation of water and salt excretion (53 to 58). However, none of the studies makes clear the cause of the diurnal variation which in normal people results in greater excretion of sodium and water during the day than during the night.

Subjects with congestive cardiac failure or cirrhosis of the liver with ascites show a reversal of the normal cycle. There is evidence that the diurnal variation is largely independent of the schedule of food intake (55). However, a higher level of sodium intake may accentuate the phenomenon (57). No good evidence has been presented that there may be a difference in adrenal activity between day and night. It seems possible that a great deal of the abnormal retention of sodium and water during the day in cardiac and cirrhotic subjects is due to stimuli such as exercise, sitting, standing, and even moving about in bed. These stimuli can lead to sodium retention, and to antidiuresis. These stimuli would not be operative at night. Studies of renal circulation (56) seem to show a larger glomerular filtration rate and renal blood flow at night in cases of edema attributable to cirrhosis and cardiac failure (55).

DIURETICS

Mercurial diuretics have been studied from several points of view. As far as site of action is concerned, there is general agreement that mercurials act primarily on the renal tubular cells. This does not mean that other factors such as the glomerular filtration rate and renal blood flow do not modify the diuretic effect. There is evidence that a low glomeruler filtration rate will diminish and an increased glomerular filtration rate will accentuate the diuresis. The effect of xanthines used in conjunction with mercurials to augment the diuresis is probably attributable to increased renal circulation (59, 60). Other factors may modify the amount of diuresis. Possibly hormonal substances which cause sodium retention by the renal tubule may thwart the effect of mercury (61). On the other hand, perhaps if enough mercury is given its effect will be uninhibited (62). The fact that mercury causes a derangement of renal tubular function is again confirmed by the demonstration that the ability of the tubules to secrete para amino hippuric acid is depressed (63). Speculation on the site of action, whether proximal or distal has been made. The evidence points to the proximal tubule (64 to 67).

Failure of the mercurials to accomplish diuresis has also been attributed to the presence of low serum concentrations of sodium and chloride. These low concentrations would diminish the load of salt presented to the tubules. Increased intake of sodium chloride augments the diuresis (68). In some pa-

tients a repeated mercurial diuresis leads to a greater deficit in chloride than of any other electrolyte (69). The responsiveness to mercurials may be restored by repair of the chloride deficit with ammonium chloride (70). One report relates that mercurial "fastness" is satisfactorily relieved by administrations of pyridoxine (71).

Augmentation of mercurial diuresis by the administration of ammonium chloride has long been used. The work of Axelrod and his co-workers (72, 73) has continued to be convincing in demonstrating that the mercurial acts primarily on the tubular reabsorption of the chloride ion. It has been a popular theory that the primary effect of ammonium chloride is to produce increased acidity and that this in turn may improve the action of mercury. It has been suggested that dissociation of the mercury ion in acid solution is better. However, the evidence is good that an alteration of acid-base balance is not necessary for the potentiation of the action of mercury (74).

The demonstration of the factors modifying the effectiveness of mercurials is helpful in explaining some of the vexing clinical problems. There are many patients who become "resistant" to mercurials, or who will not respond in the more severe, acute phases of cardiac failure. Perhaps some of the stimuli which cause sodium and water retention discussed earlier (posture, exercise, venous congestion, anxiety) also are operating in many patients to thwart the diuretic effect of mercury. In this regard, it is interesting that anoxia may interfere markedly.

The old problem of the site of action of digitalis preparations is again raised. Both Farber et al., (76) and Eichna et al. (75) are inclined to the view that there is possibly a specific effect of intravenously administered digoxin upon the kidney. This specific renal effect is in addition to whatever diuretic effect the improved renal circulation may produce. It is hardly possible to separate a primary effect on the kidney from the multiple effects of digoxin on the circulation which may in turn influence the kidney. With regard to intravenous digoxin, one wonders what direct effect the 10 per cent alcohol and the 30 per cent propylene glycol in the ampule has upon the kindey.

A somewhat promising new diuretic compound has been introduced (77, 78, 79). It is given orally and shows no evidence of renal toxicity but causes troublesome nausea and vomiting in some patients. A good diuresis is reported in at least half the patients with edema due to congestive failure of Bright's disease. The mechanism of action is probably primarily an inhibition of tubular reabsorption of sodium chloride, as with the xanthines.

Another mechanism for accomplishing diuresis which is beginning to be applied is the action of carbonic anhydrase inhibitors. Loss of sodium and "acidosis" occurred with sulfamilamide administration (80, 81) resulting from inhibition of carbonic anhydrase activity in the kidney. This led to a search for more potent inhibitors which have been used in therapy of edematous states (82 to 86). Because of the production of salt loss and acidosis it has received a trial in epilepsy (87).

The mechanism of action as diuretics of carbonic anhydrase inhibitors is the inhibition of the ability of the renal tubular cells to secrete hydrogen ions. This results in an increased loss of sodium and potassium with the production of an alkaline urine. The inability of the inhibited kidney to secrete an acid urine leads to a lowered blood pH with lowered CO_2 content. There may be a fall in serum potassium concentration and a rise in serum chlorides (88 to 91).

An effective diuresis can be produced in edematous states. However, the effectiveness rapidly diminishes with continuous administration (over eight hours). Refractoriness does not develop if the administration of single doses is spaced at daily intervals. Drowsiness, lassitude, and paresthesias are reported as side effects (84). Dangerous degrees of acidosis can be produced by the use of carbonic anhydrase inhibitors. Also, it is conceivable that a toxic depletion of potassium with low serum potassium concentration could be produced.

Thus, the carbonic anhydrase inhibitors as therapeutic diuretic agents have some of the same dangers and limitations as other agents which produce acidosis, such as ammonium chloride and exchange resins. The mercurials, the xanthines and related compounds do not have this disadvantage since secretion of acid or the addition of fixed acid is not involved. Actually, mercurials may produce a mild metabolic alkalosis attributable to greater loss of chloride and potassium with internal shifts of electrolytes.

Congenital absence of carbonic anhydrase may explain the syndrome of hyperchloremic acidosis. This condition and others which may represent congenital tubular enzymatic defects have received considerable attention recently. The typical Fanconi syndrome with inability to reabsorb certain amino acids has been studied by several workers (92, 93, 94). Detailed studies of various tubular defects are reported by Schreiner et al. (95) and Anderson et al. (96) with the demonstration of variable lesions in different members of a family. In a study of 17 patients with renal acidosis and osteomalacia, Pines & Mudge (97) suggest that a congenital tubular defect could be responsible. Jackson & Linder (98) classify the Fanconi syndrome as a "multifactorial defect" and compare it with conditions such as hyperchloremic acidosis which they consider "unifactorial." They also describe other defects such as retinal fragmentation and degeneration and deafness which sometimes accompany the renal defect.

THE KIDNEY AND HYPERTENSION

Mechanisms by which the kidney participates in the maintenance of hypertension are undoubtedly multiple, and a bewildering mass of material concerning various aspects of the problem has only clarified a small portion of it. That the adrenals are essential for the development and maintenance of experimental renal hypertension has been verified by Sevy & Wakerlin (99) and Middlesworts et al. (100) who used Goldblatt dogs. Williams et al. (101)

have obtained similar results using a perinephritis technique, and it has been shown that the adrenals are necessary for the maintenance of hypertension of both nephrectomized [Ledingham (102)] and non-nephrectomized [Hall & Hall (103)], parabiotic rats. The role of the pituitary is less clearcut, but Sevy and Wakerlin (99) found that repeated injections of crude anterior pituitary extract would lead to an antihypertensive effect in their dogs. They postulate either an antihormone effect or a direct effect, but present no evidence for either. In view of the recent observations concerning the role of the pituitary in DOCA hypertension (104, 105, 106), the antihormone concept seems possible. However, such anologies should be rigidly avoided since it is becoming more and more apparent that the hypertension produced by different experimental techniques involves markedly different mechanisms: for example, the hypertension seen in nephrectomized dogs does not require the presence of the adrenals for its development [Turner & Grollman (107, 108)], although the hypertension of nephrectomized rats can be reversed by adrenalectomy [Floyer (109)]. Species difference might also explain this discrepancy and extreme caution is advisable in interpreting the results.

Although earlier work indicated that the kidneys were not essential in the development of DOCA hypertension (110, 111), Greene and his coworkers have further studied "post DOCA" hypertension which does not depend upon the kidneys for its presence (112, 113). As previously described by Friedman and others (114, 115) this entity gradually develops in DOCA treated rats with an associated change in salt and water metabolism resulting in a state not unlike human essential hypertension. Removal of either the kidneys or the pituitary results in a reversal of the hypertension, and hypophysectomy prior to the administration of DOCA prevented the development of the syndrome (104). Progressive vascular, renal, and cardiac changes occur in this condition and it is possible that the hypertension is maintained by renal mechanisms initiated by these changes. In many respects, the animals resemble those with "fixed" hypertension following unilateral renal artery clamping (109).

The vascular changes which develop during the course of hypertension have been studied by several workers. Jones (116) has discussed the problem in some detail from the morphological standpoint, and Fertig et al. (117) have shown quite clearly that pheochromocytoma is as capable of producing progressive vascular changes as any other cause of hypertension. Goldman et al. (118) have taken periodic biopsies of the kidneys of hypertensive dogs over a five year period and have failed to show changes of the type seen in humans. There were thickening of the basement membrane of the glomerular capsule and an increase in the intercapillary substance, but the arterioles were remarkably uninvolved and changes in the juxtaglomerular apparatus such as have been described by Goormaghtigh (119) were not present. It is possible that species difference could account for this although the recent work of Knowlton et al. (120) indicates that various pressor pathways cause

varying amounts of vascular damage. They found that in adrenalectomized rats progressive vascular changes would develop during the course of hypertension due to DOCA administration whereas similar degrees of hypertension due to cortisone and salt restriction did not lead to vascular changes. It is possible that this effect is actually mediated via sodium imbalance instead of through direct hormonal activity. Tobian's observation of increased sodium content of the renal arteries of human hypertensives (121) and of rats made hypertensive with DOCA or renal ischemia (122) would support such a supposition as would the production of hypertension and vascular disease by chronic administration of salt reported by Meneely *et al.* (123). The large amounts of salt involved in this work, however, and the peculiar renal lesion produced make it difficult to evaluate its significance.

Use of antirenin in the study of renal hypertension has led to the very interesting observation that chronic Goldblatt dogs can be made normotensive by the use of the antiserum [Wakerlin (124)]. This throws new light on the pathways by which chronic hypertension is maintained in these dogs and throws considerable doubt on the supposition that renin is not responsible. In reference to this problem, it is interesting to note that Kahn *et al.* (125) have demonstrated small but definite amounts of hypertensin in the blood of human hypertensives.

NEPHRITIDES AND NEPHROPATHIES

Nephritis.—Although the problem of glomerulonephritis remains only partially solved, there has been some highly significant progress in the field recently. The relationship of streptococci to this disease has been further investigated epidemiologically and immunologically and the interrelationship somewhat clarified. Rammelkamp & co-workers (126, 127) have found that in two different groups, type 12 streptococci were associated with nephritis in a significant proportion of cases. Types 4, 18 and 25 were occasionally involved. This work is further strengthened by the review reported by Wertheim (128) in which 20 of 39 cases of acute nephritis were found to have type 12 streptococcus infections. Precise information as to how these "nephritogenic" bacteria bring about the disease is still lacking but there is little doubt but that an immunological mechanism is involved. The serum complement level has been shown to drop consistently in cases of acute nephritis (129, 130, 131), although similar changes are absent in chronic nephritis and nephrosis. Previous studies of the antistreptolysin titer in acute nephritis have been augmented by the report of Rentz (132), who found that the antistreptolysin titer is consistenlty elevated in the acute phase. As in the case of serum complement, normal values were noted in patients with chronic nephritis.

The relationship of acute nephritis to other "hyper-allergic states" has been studied from both the clinical and experimental standpoints. Previous observations of an interrelationship of acute nephritis and the Schoenlein-

Henoch syndrome have been confirmed and augmented by the reports of Philpott (133) and of Levitt & Burbank (134). In those cases of purpura and hematuria which came to autopsy, the pathologic picture in the kidney was that of typical acute glomerulonephritis. In addition, one case reported by Levitt and Burbank showed "widespread arterial lesions similar to that produced by antigen-antibody reaction in laboratory animals by numerous investigators."

The use of antikidney serum remains the only means of producing a glomerulonephritis in experimental animals. Comparison of this pathologic entity with human glomerulonephritis has led both Kobernick (135) and Ehrich *et al.* (136) to conclude that the lesions are practically the same. Ehrich takes exception to this statement in the case of nephritis in rabbits produced by horse antirabbit kidney serum in which case he says the lesion is not one of the basement membrane in the glomerulus, but one of diffuse reaction in the intercapillary space. Hill & Cruickshank (137) have described an ingenious method of study which may be useful in determining whether there really is a difference in the response of the rabbit kidney to rat serum and horse serum. These workers prepared antirat serum in rabbits and the "tagged" the antibodies with fluorescein. When injected into rats, it produced typical nephritis, and sections of the kidney revealed specific localization of the dye in the glomerular basement membrane, as well as in the basement membrane of the renal tubules and in a reticular network in the media of blood vessels. The ultramicroscopic studies of Rinehart *et al.* (138) and Hall (139) suggest that this basement membrane is of endothelial origin. Simonsen (140) compares these endothelial cells with semi-differentiated mesenchymal cells of the reticuloendothelial system and suggests that their reaction in nephritis is similar to the reaction of reticuloendothelial cells to antigens leading to the production of plasma cells. Jones (141), on the other hand, considers the glomerular reaction a nonspecific one of inflammation similar to that seen in any part of the body.

The clinical problem of nephritis has received less attention than the experimental problem recently. Peters (142) has discussed the problem of edema in acute nephritis, and reviewed in considerable detail 291 cases of nephritis seen at the New Haven Hospital over a 30 year period. He concluded that congestive heart failure is responsible for the edema and that appropriate therapy should be directed toward the heart. Newburgh & Camara (143) emphasize the lack of correlation between the clinical signs and symptoms and the degree of renal involvement and Sarre & Mahr (144) concluded from a study of 64 patients that prognosis could not be determined with accuracy during the acute phase. Kellett (131) was unable to relate changes in serum complement level to either prognosis or severity of the disease.

Prophylaxis appears to be the most valuable treatment for nephritis. Stetson and his co-workers (127) report that penicillin administration ap-

peared to prevent the subsequent development of acute nephritis in 50 patients who had type 12 streptococci infections. Gamma globulin, on the other hand, was given to 30 such patients with the subsequent development of acute nephritis in 6 cases. If confirmed, this work will prove highly significant.

Therapy of active nephritis remains unsatisfactory. Baldwin *et al.* (145), in a study of the value of nitrogen mustards, noted temporary remissions of from 3 to 12 days in 22 of 41 courses given to patients with chronic glomerulonephritis, and in acute nephritis, one patient out of five treated appeared to go on to complete healing. No harmful effects were observed and these workers feel that further study is indicated. Less encouraging results were obtained by Boyd & Commons (146) who gave nitrogen mustards to 10 patients with no apparent benefit. Etteldorf & Tuttle (147) have studied the effect of intravenous magnesium sulfate upon renal function and have found no change in glomerular filtration rate or tubular excretory capacity despite a moderate increase in renal plasma flow. Trevisini (148) found no beneficial response to the infiltration of the renal pedicle with procaine.

Nephrosis.—The theory that nephrosis is a form of glomerulonephritis has been given new support by the experimental work of Ehrich *et al.* (136, 149) in which small doses of anti-kidney serum produced a nephrotic syndrome in rats and rabbits. Larger doses of the same serum produced typical nephritis. The latent period between the injection of serum and the development of disease which is typical in the case of nephritis was not observed in the case of nephrosis, however, and immunological studies failed to reveal abnormalities of serum complement or antistreptolysin such as are typical of nephritis (129, 130, 132). The exact relationship between the two entities remains obscure.

Nephrosis has received considerable attention from the clinical standpoint. Numerous reports on the use of cortisone or ACTH have appeared (150 to 158), with the general conclusion that over half of the cases will respond satisfactorily. There appears to be no reliable means of determining which patients will respond. Merrill (151, 152) reports that the use of ACTH Gel on alternate days will control practically all cases, but until his few cases have been greatly augmented, no conclusion can be drawn.

Other types of treatment of nephrosis which have been studied include malaria (159, 160) and nitrogen mustards (146, 161, 162), neither of which proved particularly effective. Resins have been used to aid in the control of edema (163) but have no effect on the underlying disease.

Bjørneboe *et al.* (164, 165) have followed the clinical course of nephrosis by means of renal biopsy and have shown a marked lack of correlation between microscopic picture and albuminuria. The NPN[2] and microscopic picture correlated well, however. Another interesting study was made by Recant & Riggs (166) who found a diminished protein bound iodine in 13 of 16 cases of nephrosis. Iodine uptake and percentage retention of iodine were

normal, however, and it was concluded that nephrotics do not lose enough thyroid hormone to produce hypothyroidism.

Pyelonephritis.—Pyelonephritis has received considerable attention in reference to etiology, therapy, and relation to hypertension, but few advances have been made. A remarkable family is reported by Perkoff *et al.* (167) in which 50 male members developed a chronic interstitial nephritis of the type originally described by Weiss & Parker (168). They raise the question of hereditary factors and comment on the fact that only males developed progressive renal failure in this family. The more classical incrimination of ascending infection is defended by Barnard & co-workers (169) who found that 51 of 52 diabetic patients with urinary tract infection were females. The relationship of pyelonephritis to arterial hypertension has been further studied by Saphir & Taylor (170) who were able to demonstrate evidence of pyelonephritis in 49 out of 50 cases who died with malignant hypertension. In 43 of the 49, the lesion was that of typical chronic pyelonephritis. Three had acute pyelonephritis and three had only slight chronic changes. Should this work be confirmed, it will alter considerably our concepts of malignant hypertension.

The problem of treatment of pyelonephritis has been discussed by Stenderup *et al.* (171) and by Womack *et al.* (172). In view of the current status of antibiotics and chemotherapy, it is remarkable that failure is so common, but numerous reports using all available drugs emphasize the difficulties and frequent relapses (173, 174, 175). The significance of heredity, previous injury, obstruction, diabetes, and unknown factors remain to be clarified.

Papillary necrosis as a complication of renal infection has been discussed in detail by Mandel (176) and 22 more cases have been added to the 160 reviewed by Mandel (177 to 181). It is generally agreed that papillary ischemia attributable to thrombosis, shock, dehydration, or unknown factors is responsible for the lesion, although infection is practically always present. Diabetes or obstruction is usually present, but that neither is absolutely necessary is evidenced by the 8 week old infant reported by Tmaki & Whitman (181) who developed hemorrhagic papillitis without any pre-existing lesion. Two of the patients reported by Silberstein & Paugh (178) also had neither diabetes nor obstruction.

Acute Renal Failure.—In an extensive study, Oliver, MacDowell & Tracy (182) have presented a comprehensive concept of acute renal failure which has done much to correlate the mass of confusing material which has accumulated during the past few years. Using a microdissection technique, they demonstrated two basic types of acute tubular injury and related these to the cause. Shock, the principle clinical cause of acute renal failure, led to a diffuse, unpredictable lesion which was variable from nephron to nephron. Blood borne toxins such as carbon tetrachloride [as discussed by Partenheimer & Citron (183)] however, produced a uniform lesion in each nephron.

Combinations of toxins and ischemia such as might occur in crush injuries caused unending combinations of the two lesions.

Both Oliver's work and the work of Terri & Goreni (184) tend to show that blocked tubules are not responsible for the lesions of acute renal failure. Shock, on the other hand, is a common cause. Block *et al.* (185) present convincing experimental evidence of this and it is emphasized by Moon (186) in his concise review of the subject. It is probable that shock with associated anoxia was responsible for the case of lower nephron nephrosis due to the Waterhaus-Friderichsen syndrome reported by Walker *et al.* (187). Gaberman *et al.* (188) present 22 cases in which renal anoxia appeared to lead to acute renal failure and Bernstein *et al.* (189) discuss the possibility that transient impairment of renal function in diabetics recovering from coma is probably a manifestation of mild lower nephron nephrosis. It seems likely that most if not all of the renal manifestations of Epidemic Hemorrhagic Fever as reported from Korea and Japan (190 to 194) are actually manifestations of acute renal failure rather than a specific renal disease. Certainly shock is a prominent feature of the disease although the characteristic diffuse vascular lesion may play a direct part in the renal aspects of the disease.

The management of acute renal failure has received considerable attention recently. Swann & Merrill have reviewed in detail the usual clinical course of the disease (195) and the profound electrolyte disturbances which can occur are emphasized by many authors (196 to 200). It is generally agreed that dialysis is only of moderate value and probably does not appreciably alter mortality (201), although Alwall *et al.* (202) feel that dialysis has been lifesaving in a number of their cases. When used, its principle value is in reversing hyperkalemia.

Prognosis of acute renal failure has been studied by several workers (203, 204, 205) with the general conclusion that recovery is usually complete although occasionally there is slight residual impairment of renal blood flow, glomerular filtration rate, and maximum concentrating ability.

RENAL TRANSPLANT

Successful transplant of the kidney still has not been accomplished, although two of six human cases reported by Hume *et al.* (206, 207) functioned considerably longer than any reported homotransplants in animals. Donor kidneys used by these workers were ischemic from 14 to 205 min. and it is interesting to note that the most encouraging result was obtained in the kidney which was ischemic the longest. All transplants eventually failed from infection with variable intravascular thrombosis. Similar changes were observed by Muirhead (208) in dogs after a period of about 10 days during which the kidneys functioned quite well. This problem has been discussed in considerable detail by Simonsen *et al.* (209) with the conclusion that destruction of the transplant occurs because of antibodies formed by the recipi-

ent. This work is supported by the observations of Favour *et al.* (210) that serum complement frequently rises following renal transplant. The toxic syndrome described by Dempster (211) in dogs with homotransplanted kidneys may be part of this reaction, although when observed in dogs with auto-transplants it appears to be a result of infection.

LITERATURE CITED

1. Holland, D. C., and Stead, E. A., Jr., *Arch. Internal Med.*, **88,** 571 (1951)
2. Weston, R. E., Hanenson, I. B., Grossman, J., Berdasco, G. A., and Wolfman, M., *J. Clin. Invest.*, **32,** 611 (1953)
3. Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, O., *J. Clin. Invest.*, **32,** 582 (1953)
4. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C., *J. Clin. Invest.*, **30,** 862 (1951)
5. Weston, R. E., Hanenson, I. B., Borun, E. R., Grossman, J., and Wolfman, M., *J. Clin. Invest.*, **31,** 672 (1952)
6. Weston, R. E., Hanenson, I. B., Grossman, J., Borun, E. R., Wolfman, M., and Leiter, L., *Federation Proc.*, **12,** 153 (1953)
7. Leaf, A., Mamby, A. R., Rasmussen, H., and Marasco, J. P., *J. Clin. Invest.*, **31,** 914 (1952)
8. Tarail, R., and Longsdon, G. R., *J. Clin. Invest.*, **32,** 607 (1953)
9. Leaf, A., and Mamby, A. R., *J. Clin. Invest.*, **31,** 60 (1952)
10. Leaf, A., and Mamby, A. R., *J. Clin. Invest.*, **31,** 54 (1952)
11. Welt, L. G., and Orloff, J., *J. Clin. Invest.*, **30,** 751 (1951)
12. Tetersdorf, R. G., and Welt, L. G., *J. Clin. Invest.*, **32,** 283 (1953)
13. Goodyer, A. V. N., and Feldin, D. W., *J. Clin. Invest.*, **32,** 242 (1953)
14. Wyndham, C. H., Bouwer, W. V. D. M., Devine, M. D. and Patterson, H. E., *J. Appl. Physiol.*, **5,** 285 (1953)
15. Judson, W. E., Hatcher, J. D., Halpern, M. H., and Wilkins, R. S., *J. Clin. Invest.*, **31,** 642 (1952)
16. Frieden, J., Rice, L., Elisberg, E. I., Eisenstein, B., and Katz, L. N., *Am. J. Physiol.*, **168,** 650 (1952)
17. Lusk, J. A., Viar, W. N., and Harrison, T. R., *Circulation*, **6,** 811 (1952)
18. Rosenbaum, J. D., Papper, S., and Ashley, M. M., *J. Clin. Invest.* **31,** 657 (1952)
19. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., Rossmeisl, E. C., *J. Clin. Invest.*, **31,** 80 (1952)
20. Stamler, J., Goldberg, H., Gordon, A., Weinshel, M., and Katz, L. N., *Am. J. Physiol.*, **166,** 400 (1951)
21. Holland, B. C., *J. Clin. Invest.*, **31,** 639 (1952)
22. Friberg, O., *Acta Endocrinol.*, **12,** 193 (1953)
23. Erankó, O., Friberg, O., and Karvonen, M. J., *Acta Endocrinol.*, **12,** 197 (1953)
24. Rosenbaum, J. D., Nelson, W. P., III, Strauss, M. B., Davis, R. K., and Rossmeisl, E. C., *J. Clin. Invest.*, **32,** 394 (1953)
25. Levitt, M. F., Turner, L. D., and Sweet, A. Y., *J. Clin. Invest.*, **31,** 885 (1952)
26. Chalmers, T. M., Lewis, A. A. G., and Pawan, G. L. F., *J. Physiol. (London)* **117,** 218 (1952)
27. Hinkle, L. E., Jr., Edwards, C. J., Wolf, F., *J. Clin. Invest.*, **30,** 809 (1951)
28. Miles, B. E., DeWardener, H. E., McSwiney, R. R., *Am. J. Med.*, **12,** 659 (1952)
29. Leimdorfer, A., *Federation. Proc.*, **12,** 84 (1953)
30. Dexter, D., and Stoner, H. B., *J. Physiol.*, **118,** 486 (1952)
31. Eversole, W. J., Giere, F. A., and Rock, M. H., *Am. J. Physiol.*, **170,** 24 (1952)
32. Mills, L. C., Skelton, J., and Moyer, J. H., *Am. J. Med.*, **13,** 648 (1952)
33. Dearborn, E. H., and Lasagna, L., *J. Pharmacol. Exptl. Therap.*, **106,** 122 (1952)
34. Newman, E. V., *Proc. of New Engl. Cardiovascular Soc.*, **11,** 31 (1953)

35. Bachman, D. M., and Youmans, W. B., *Circulation*, **7**, 413 (1953)
36. Lombardo, G. A., *Circulation*, **7**, 91 (1953)
37. Davis, J. O., and Howell, D. S., *Circulation Research*, **1**, 171 (1953)
38. Lombardo, T. A., and Harrison, T. R., *Circulation*, **7**, 88 (1953)
39. Epstein, F. H., Post, I. S., McDowell, M. E., and Shadle, O. W. and Ferguson, T. D., *Am. J. Med.*, **14**, 503 (1953)
40. Pearce, M. L., and Newman, E. V., *J. Clin. Invest.*, **32**, 594 (1953)
41. Dochosis, M., and Dreifus, L. F., *Am. J. Med. Sci.*, **222**, 538 (1951)
42. White, A. G., Rubin, G., and Leiter, L., *J. Clin. Invest.*, **30**, 1287 (1951)
43. White, A. G., and Rubin, G., *J. Clin. Invest.*, **31**, 673 (1952)
44. Nelson, W. P., and Welt, L. G., *J. Clin. Invest.*, **31**, 392 (1952)
45. Miller, G. E., and Townsend, C. E., *J. Clin. Invest.*, **32**, 590 (1953)
46. Luetscher, J. A., Jr., and Johnson, B. B., *J. Clin. Invest.*, **32**, 585 (1953)
47. Gordon, E. S., Chart, J. J., and Meyer, E. S., *J. Clin. Invest.*, **31**, 633 (1952)
48. Chart, J. J., and Shipley, E. S., *J. Clin. Invest.*, **32**, 560 (1953)
49. Smythe, C. M., Nickel, J. S., and Bradley, S. E., *J. Clin. Invest.*, **31**, 499 (1952)
50. Lauson, H. D., and Thompson, D. D., *Federation Proc.*, **12**, 83 (1953)
51. Judson, W. E., Hollander, W., Friedman, I. H., Hatcher, J. D., and Halpern, M. H., *J. Clin. Invest.*, **32**, 579 (1952)
52. Duncan, L. E., Jr., Solomon, D. H., Nichols, M. P., and Rosenberg, E., *J. Clin. Invest.*, **30**, 908 (1951)
53. Goldman, R., and Bassett, S. H., *Am. J. Med.*, **13**, 93 (1952)
54. Rosenbaum, J. D., Ferguson, B. C., Davis, R. K., and Rossmeisl, E. C., *J. Clin. Invest.*, **31**, 507 (1952)
55. Goldman, R., *J. Clin. Invest.*, **30**, 1191 (1951)
56. Jones, R. A., McDonald, G. O., and Last, J. H., *J. Clin. Invest.*, **31**, 326 (1952)
57. Papper, S., and Rosenbaum, J. D., *J. Clin. Invest.*, **31**, 401 (1952)
58. Mills, J. N., and Stanbury, S. W., *J. Physiol.*, **117**, 22 (1952)
59. Kupfer, S., Thompson, D. D., and Pitts, R. F., *Am. J. Physiol.*, **167**, 603 (1951)
60. Weston, R. E., Eschler, E. J. W., Grossman, J., and Leiter, L., *J. Clin. Invest.*, **31**, 901 (1952)
61. Axelrod, D. R., and Pitts, R. S., *Am. J. Physiol.*, **169**, 350 (1952)
62. Farah, A. E., *Proc. Soc. Exptl. Biol. Med.*, **80**, 295 (1952)
63. Weston, R. E., Grossman, J., Lehman, R. A., Ullman, T. D., Halpern, J. B., and Leiter, L., *J. Clin. Invest.*, **30**, 1221 (1951)
64. Welt, L. G., Goodyer, A. V. N., Darragh, J. H., Abele, W. A., and Meroney, W. H., *J. Clin. Invest.*, **31**, 671 (1952)
65. Weston, R. E., Grossman, J., and Leiter, L., *J. Clin. Invest.*, **30**, 1262 (1951)
66. Brodsky, W. A., and Graubarth, H. N., *Am. J. Physiol.*, **172**, 67 (1953)
67. Rice, L., Frieden, J., Smith, M., and Kaplan, B., *J. Clin. Invest.*, **32**, 657 (1952)
68. Farah, A., Cobbey, S., and Mook, W., *J. Pharmacol. Exptl. Therap.* **104**, 31 (1952)
69. Stapleton, J. F., and Harvey, W. P., *Arch. Internal. Med.*, **90**, 425 (1952)
70. Schwarts, W. D., and Wallace, W. M., *J. Clin. Invest.*, **30**, 1089 (1951)
71. Waldman, S., and Pelner, L., *Am. J. of Med. Sci.*, **225**, 39 (1953)
72. Axelrod, D. R., and Pitts, R. F., *J. Clin. Invest.*, **31**, 171 (1952)
73. Catts, J. N., Wiggins, W. S., Axelrod, D. R., and Pitts, R. F., *Circulation*, **6**, 82 (1952)
74. Hilton, J. G., *J. Clin. Invest.*, **30**, 1105 (1951)

75. Eichna, L. W., *et al.*, *J. Clin. Invest.*, **30**, 1250 (1951)
76. Farber, S. J., Alexander, J. D., Pellegrino, E. D., and Earle, D. T., *Circulation*, **4**, 378 (1951)
77. Kattus, A., Arrington, T. M., and Newman, E. V., *Am. J. Med.*, **12**, 319 (1952)
78. Spencer, A. G., *Brit. Med. J.*, **I**, 957 (1953)
79. Hellman, E., Altchek, R., and Enselberg, C. D., *Am. Heart J.*, **44**, 615 (1952)
80. Wood, W. B., Jr., and Favour, C. B., *J. Clin. Invest.*, **20**, 433 (1941)
81. Roughton, F. J. W., Dill, D. W., Darling, R. C., Graybiel, A., Kneler, C. A., and Talbott, J. H., *Am. J. Physiol.*, **135**, 77 (1941)
82. Taymor, R. C., and Halpern, M., and Friedberg, C. K., *Am. J. Med.*, **14**, 531 (1953)
83. Berliner, R. W., Kennedy, D. J., Jr., and Orloff, J., *Am. J. Med.*, **11**, 274 (1951)
84. Friedberg, C. K., Taymor, R., Minor, J. B., Halpern, M., *New Engl. J. Med.*, **248**, 883 (1953)
85. Maren, T. H., *Trans. N. Y. Acad. Sci.*, **15**, 53 (1952)
86. Metcoff, J., James, J. A., and Gordillo, G., *J. Clin. Invest.*, **32**, 590 (1953)
87. Bergstrom, W. K., Gorzoli, R. F., Lombroso, C., Davidson, D. T., and Wallace, W. M., *Am. J. Diseases Children*, **84**, 771 (1952)
88. Nadell, J., *J. Clin. Invest.*, **32**, 622 (1953)
89. Friedberg, C. K., Halpern, M., and Taymor, R., *J. Clin. Invest.*, **31**, 1074 (1952)
90. Shideman, F. E., Rathbun, R. C., and Stoneman, F., *Am. J. Physiol.*, **170**, 31, (1952)
91. Schwartz, W. B., Danzig, L. E., and Relman, A. S., *Am. J. Med.*, **14**, 526 (1953)
92. Harper, H. A., Grossman, M., Henderson, P., and Steinbach, H., *Am. J. Diseases Children*, **84**, 327 (1952)
93. Milne, M. D., Stanbury, S. W., and Thomson, A. E., *Quart. J. Med.*, **21**, 61 (1952)
94. Sirota, J. H., Yü, T. F., and Gutman, A. B., *J. Clin. Invest.*, **31**, 692 (1952)
95. Schreiner, G. E., Smith, L. H., and Kyle, L. H., *Am. J. Med.*, **15**, 122 (1953)
96. Anderson, I. A., Miller, A., and Kenny, A. P., *Quart. J. Med.*, **21**, 33 (1952)
97. Pines, K. L., and Mudge, G. H., *Am. J. Med.*, **11**, 302 (1951)
98. Jackson, W. P. U., and Linder, G. C., *Quart. J. Med.*, **22**, 133 (1953)
99. Sevy, R. W., and Wakerlin, G. E., *Am. J. Physiol.*, **172**, 129 (1953)
100. Middlesworts, L. Z., Tyson, W. T., and Segal, M., *Federation Proc.*, **12**, 147 (1953)
101. Williams, W., Whisnant, C., and Fitts, W. T., Jr., *Am. J. Physiol.*, **170**, 57 (1952)
102. Ledingham, J. M., *Clin. Sci.*, **10**, 423 (1951)
103. Hall, C. E., and Hall, O., *Am. J. Physiol.*, **173**, 29 (1953)
104. Greene, D. M., Saunders, F. J., Wallgren, N., McDonough, F. J., and Clampit, J. M., *Am. J. Physiol.*, **170**, 107 (1952)
105. Handler, P., and Bernheim, F., *Am. J. Physiol.*, **166**, 528 (1951)
106. Friedman, S. M., Friedman, C. L., and Nakashima, M., *Am. J. Physiol.*, **170**, 270 (1952)
107. Turner, L. B., and Grollman, A., *Am. J. Physiol.*, **166**, 185 (1951)
108. Turner, L. B., and Grollman, A., *Am. J. Physiol.*, **167**, 462 (1951)
109. Floyer, M. A., *Clin. Sci.*, **10**, 405 (1951)
110. Friedman, S. M., and Friedman, C. L., *J. Exptl. Med.*, **89**, 631 (1949)
111. Hall, C. E., and Hall, O., *Proc. Soc. Exptl. Biol. Med.*, **71**, 690 (1949)

112. Greene, D. M., Saunders, F. J., Wahlgren, N., and Craig, R. L., *Am. J. Physiol.*, **170**, 94 (1952)

113. Greene, D. M., Craig, R. L., Ponder, F. J., and Sturtevant, F. M., *Am. J. Physiol.*, **170**, 477 (1952)

114. Friedman, S. M., and Friedman, C. L., *Can. Med. Assoc. J.*, **61**, 596 (1949)

115. Prado, J. L. (Doctoral thesis, Sao Paulo, Brazil, 1950)

116. Jones, D. B., *Am. J. Pathol.*, **29**, 619 (1953)

117. Fertig, H. H., Taylor, R. D., Corcoran, A. C., and Page, I. H., *Ann. Internal Med.*, **35**, 1358 (1951)

118. Goldman, M. L., Schroeder, H. A., and Damin, G. J., *Am. J. Med.*, **14**, 751 (1953)

119. Goormaghtigh, N., *J. Urol. Med. Chir.*, **157**, 569 (1951)

120. Knowlton, A. I., Loeb, N., Stoerk, H. C., White, J. P., and Heffern, J. F. *J. Exptl. Med.*, **96**, 187 (1952)

121. Tobian, L., Jr., and Binion, J., *Am. J. Med.*, **12**, 107 (1952)

122. Tobian, L., Jr., and Binion, J., *J. Clin. Invest.*, **32**, 608 (1953)

123. Meneely, G. R., Tucker, R. G., Auerbach, S. H., and Darby, W. J., *J. Clin. Invest.*, **31**, 650 (1952)

124. Wakerlin, G. E., Bird, R. V., Bernan, B. B., Frank, M. H., Kremen, S., Kuperman, I., and Skom, J. H., *J. Lab. Clin. Med.*, **41**, 709 (1953)

125. Kahn, J. R., Skeggs, L. T., Jr., Shumway, N. P., and Wisenbaugh, P. E., *J. Exptl. Med.*, **95**, 523 (1952)

126. Rammelkamp, C. H., Jr., and Weaver, R. S., *J. Clin. Invest.*, **32**, 345 (1953)

127. Stetson, C. A., Rammelkamp, C. H., Perry, W. B., Krause, R. M., and Kohen, R. J., *J. Clin. Invest.*, **32**, 606 (1953)

128. Wertheim, A. R., Lyttle, J. D., Loeb, E. N., Earle, D. P., Jr., Seegal, B. C., and Seegal, D., *J. Clin. Invest.*, **32**, 359 (1953)

129. Lange, K., Greig, F., Overman, J., Slobody, L., Ogur, G., and Locasto, F., *Arch. Internal Med.*, **88**, 433 (1951)

130. Fischel, E. E., and Gajdusek, D. C., *Am. J. Med.*, **12**, 190 (1952)

131. Kellett, C. E., *Lancet*, **II**, 911 (1952)

132. Rentz, L. A., DiCaprio, J. M., and Randall, E., *Am. J. Med. Sci.*, **224**, 194 (1952)

133. Philpott, M. G., *Arch. Disease Childhood*, **27**, 480 (1952)

134. Levitt, L. M., and Burbank, B., *New Engl. J. Med.*, **248**, 530 (1953)

135. Kobernick, S. D., *Am. J. Med. Sci.*, **224**, 329 (1952)

136. Ehrich, W. E., Forman, C. W., and Seifer, J., *Arch. Pathol.*, **54**, 463 (1952)

137. Hill, A. G. S., and Cruickshank, B., *Brit. J. Exptl. Pathol.*, **34**, 27 (1953)

138. Rinehart, J. F., Faraquhart, M. G., Jung, H. C., and Abul-Hag, S. K., *Am. J. Pathol.*, **29**, 21 (1953)

139. Hall, B. V., *Federation Proc.*, **12**, 467 (1953)

140. Simonsen, M., *Acta Pathol. Microbiol. Scand.*, **32**, 85 (1953)

141. Jones, D. B., *Am. J. Pathol.*, **29**, 33 (1953)

142. Peters, J. P., *Am. J. Med.*, **14**, 448 (1953)

143. Newburgh, L. H., and Camara, A. A., *Ann. Internal Med.*, **35**, 39 (1951)

144. Sarre, H., and Mahr, H., *Deutsche med. Wochschr.*, **77**, 522 (1952)

145. Baldwin, D. S., McLean, P. G., Chasis, H., and Goldring, W., *Arch. Internal Med.*, **92**, 162 (1953)

146. Boyd, I. I., and Commons, R. I., *Am. J. Med.*, **13**, 499 (1952)

147. Etteldorf, J. N., and Tuttle, A. J., *J. Pediat.*, **41**, 524 (1952)
148. Trevisini, A., *Urologia*, **19**, 71 (1952)
149. Ehrich, W. E., *Zentr. allgem. Pathol. u. pathol. Anat.*, **89**, 354 (1952)
150. Riley, C. M., *J. Am. Med. Assoc.*, **150**, 1288 (1952)
151. Merrill, A. J., and Mitchell, G. L., Jr., *J. Clin. Invest.*, **32**, 589 (1953)
152. Merrill, A. J., *Am. J. Med.*, **14**, 755 (1953)
153. Luetscher, J. A., Jr., Deming, Q. B., and Johnson, V. B., *J. Clin. Invest.*, **30**, 1530 (1951)
154. Keith, M. M., Power, M. H., Daugherty, B. W., and Keith, H. M., *Arch. Internal Med.*, **89**, 689 (1952)
155. Riley, C. M., *Bull. N. Y. Acad. Med.*, **28**, 630 (1952)
156. Fellinger, K., Falkner, R., Lachnit, V., and Watschinger, D., *Deut. Arch. klin. Med.*, **199**, 481 (1952)
157. McCall, F. M., Roth, A., Wolkan, B., Burns, A. D., Harper, E. M., and Boldbloom, A., *Arch. Disease Childhood*, **27**, 309 (1952)
158. Arneil, G. C., and Wilson, H. D. C., *Arch. Disease Childhood*, **27**, 322 (1952)
159. Gairdner, D., *Lancet*, **I**, 842 (1952)
160. Byrne, E. A. J., *Lancet*, **I**, 844 (1952)
161. Kelley, V. C., and Panos, T. C., *J. Pediat.*, **41**, 505 (1952)
162. Kelley, V. C., and Panos, T. C., *J. Pediat.*, **41**, 518 (1952)
163. Lippman, R. W., *Arch. Internal Med.*, **88**, 9 (1951)
164. Bjørneboe, M., Brun, C., Gromsen, H., Iversen, P., and Raschou, F., *Acta Med. Scand.*, Suppl. **266**, 249 (1952)
165. Bjørneboe, M., Brun, C., Gromsen, H., Iversen, P., and Raschou, F., *Acta Med. Scand.*, Suppl., **266**, 233 (1953)
166. Recant, L., and Riggs, D. S., *J. Clin. Invest.*, **31**, 789 (1952)
167. Perkoff, G. E., Stephens, S. E., Dolowitz, D. A., and Tyler, S. H., *Arch. Internal Med.*, **88**, 191 (1951)
168. Weiss, S., and Parker, F., *Medicine*, **18**, 221 (1939)
169. Barnard, D. M., Storey, R. D., and Root, H. F., *New Engl. J. Med.*, **248**, 136 (1953)
170. Saphir, O., and Taylor, B., *Ann. Internal Med.*, **36**, 1017 (1952)
171. Stenderup, A., Kissmeyer-Nielsen, F., and Linnet-Jepsen, P., *Acta Med. Scand.*, **144**, 124 (1952)
172. Womack, C. R., Jackson, G. G., Gocke, T. M., Kass, E. H., Haight, T. H., and Finland, M., *Arch. Internal Med.*, **89**, 240 (1952)
173. Norfleet, C. M., Jr., Beamer, P. R., and Carpenter, H. M., *J. Urol.*, **70**, 113 (1953)
174. Hopper, J., Jr., Jawetz, E., and Hinman, F., Jr., *Am. J. Med. Sci.*, **225**, 402 (1953)
175. Fisher, P., *Ann. Internal Med.*, **35**, 1117 (1951)
176. Mandel, E. E., *Am. J. Med.*, **13**, 322 (1952)
177. Knutsen, A., Jennings, E. R., Brines, O. A. and Axelrod, A., *Am. J. Clin. Pathol.*, **22**, 327 (1952)
178. Silberstein, J. S., and Paugh, J. T., *Ann. Internal Med.*, **38**, 689 (1953)
179. Johnston, D. H., *Arch. Internal Med.*, **90**, 711 (1952)
180. Slipyan, A., and Barland, S., *J. Urol.*, **68**, 430 (1952)
181. Tmaki, H. T., and Whitman, M. A., *J. Am. Med. Assoc.*, **150**, 1304 (1952)
182. Oliver, J., MacDowell, M., and Tracy, A., *J. Clin. Invest.*, **30**, 1307 (1951)

183. Partenheimer, R. C., and Citron, D. S., *Arch. Internal Med.*, **89** 216 (1952)
184. Terri, G. C., and Goreni, P., *Brit. J. Exptl. Pathol.*, **33**, 440 (1952)
185. Block, M. A., Wakim, K. G., and Mann, F. C., *Arch. Pathol.*, **54**, 443, 1952
186. Moon, V. H., *Ann. Internal Med.*, **39**, 51 (1953)
187. Walker, S. H., Cavenaugh, R. L., and Williams, H., *Ann. Internal Med.*, **38**, 610 (1953)
188. Gaberman, P., Atlas, D. H., Kammerling, E. M., Ehrlich, L., and Isaacs, J., *Ann. Internal Med.*, **35**, 148 (1951)
189. Bernstein, L. M., Foley, E. F., and Hoffman, W. F., *J. Clin. Invest.*, **31**, 711 (1952)
190. Katz, S., Leedham, C. L., and Kessler, W. H., *J. Am. Med. Assoc.*, **150**, 1363 (1952)
191. Barbero, G. J., Katz, S., Kraus, H., and Leedham, C. L., *Arch. Internal Med.*, **91**, 177 (1953)
192. Mayer, C. F., *Lab. Invest.*, **1**, 291 (1952).
193. Symposium on Epidemic Hemorrhagic Fever, *Ann. Internal Med.*, **38**, 53 (1953)
194. Andrew, R., *Brit. Med. J.*, **I**, 1063 (1953)
195. Swann, R. C., and Merrill, J. P., *Medicine*, **32**, 215 (1953)
196. Hunter, R. B., and Muirhead, E. E., *Ann. Internal Med.*, **36**, 1297 (1952)
197. Iseri, L. T., Batchelor, T. M., Boyle, A. J., and Myers, G. B., *Arch. Internal Med.*, **89**, 188 (1952)
198. Callaway, J. J., and Roemmich, W., *Ann. Internal Med.*, **37**, 784 (1952)
199. Berglund, F., Ek, J., and Werko, L., *Acta. Med. Scand.*, **144**, 399 (1953)
200. Vest, S. A., and Kelley, I. A., *J. Urol.*, **69**, 55 (1953)
201. Snapper, I., *Bull. N. Y. Acad. Med.*, **28**, 621 (1952)
202. Alwall, N., Lunderquist, A., and Tornberg, A., *Nord. Med.*, **48**, 1554 (1952)
203. Lowe, K. G., *Lancet*, **I**, 1086 (1952)
204. Finkenstaedt, J. T., O'Meara, M. P., Waller, J. M., and Merrill, J. P., *J. Clin. Invest.*, **32**, 567 (1953)
205. Andersen, A. H., and Baden, H., *Acta Med. Scand.*, *Suppl.*, **266**, 161 (1952)
206. Hume, D. M., Merrill, J. P., and Miller, B. F., *J. Clin. Invest.*, **31**, 640 (1952)
207. Hawn, C. V. Z., Hume, D. M., Merrill, J. P., and Miller, B. F., *Federation Proc.*, **12**, 391 (1953)
208. Muirhead, E. E., *Am. J. Med.*, **13**, 649 (1952)
209. Simonsen, M., Buemann, J., Gammeltost, A., Jensen, F., and Jorgensen, K., *Acta Pathol. Microbiol. Scand.*, **32**, 1 (1953)
210. Favour, C. B., Murray, J. E., Wemyss, C. T., Jr., Colodny, A., and Miller, B. F., *Proc. Soc. Exptl. Biol. Med.*, **83**, 352 (1953)
211. Dempster, W. J., *Acta. Med. Scand.*, **144**, 360 (1953)

DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY

PURPURA: A REVIEW OF SELECTED ASPECTS OF THE HEMORRHAGIC DISORDERS[1,2,3]

By Mario Stefanini[4] and William Dameshek

Blood Research Laboratory of the New England Center Hospital, and the Department of Medicine, Tufts College Medical School, Boston, Massachusetts

Introduction

The subject of purpura has become greatly involved in the course of the last few years, as a number of significant observations have been reported, particularly in the fields of the thrombocytopenic states and the coagulation mechanisms. The present review will be necessarily limited to some aspects of this subject which have undergone developments of particular clinical significance. Thrombocytopenic states, fibrinolysis, and certain disorders of the blood coagulation mechanisms will be discussed in detail. Other phases of the subject of purpura have been discussed in many excellent reviews. Monographs on the progressively more complicated field of blood coagulation have been written by Burstein (1), Quick (2), and Biggs & Macfarlane (3). Seegers has summarized his concepts and those of his co-workers in a 1952 Harvey lecture (4). A series of seminars in the *American Journal of Medicine* has covered some aspects of purpura, with articles on basic mechanisms of blood coagulation (5), mechanism of prothrombin conversion (6), hemophilia (7), idiopathic thrombocytopenic purpura (8), and allergic purpura (9). The vascular factor of hemostasis has been discussed in detail in Roskam's monograph (10) and in Spaet's review article (11). Clark & Jacobs (12) have presented interesting results by Japanese investigators on the effect of antiblood vessel serum experimentally produced in animals. A stimulating article by Humble (13) has described the mechanism of petechial formation in thrombocytopenic patients by the ingenious technic of studying the nail bed capillaries with the microscope under conditions that are created in the performance of the tourniquet test. Humble's results appear to confirm that simple extravasation of blood is the basic mechanism in petechial formation. By studying capillaries in patients with hemolytic thrombotic thrombocytopenia (thrombotic thrombocytopenic purpura), however, Orbi-

son (14) has revived the old theory that formation of aneurysms in the vascular wall represents at least one phase of the formation of petechiae. This controversy again emphasizes the great need for a better and more complete understanding of the vascular mechanism of hemostasis. Readers particularly interested in this subject are referred to a series of articles by Chambers & Zweifach (15, 16, 17) and Lutz (18).

Although no rigid criteria can be drawn as to the varying pathogenetic mechanisms of purpura, it is convenient to differentiate this disturbance into certain compartments or types. This should only be done with the knowledge that, although a given case of purpura may be designated as belonging to a certain type, there is frequently an overlapping with other types of pathogenetic mechanisms. Nevertheless, the fundamental or important mechanism usually gives the name to the type of purpura, and as of now, the following classification of the purpuras may be offered: (a) Thrombocytopenic —in which reduction in blood platelets is the chief cause for the hemorrhagic disorder. (b) Vascular—attributable to defects of the blood vessel wall and including many disorders in which the fundamental feature is injury to the endothelial surface of the capillary or small blood vessel. (c) Coagulation defect—in which the outstanding feature is a disturbance in the clotting mechanism. (d) Fibrinolytic—in which excessive fibrinolysis is the preeminent cause of bleeding. The rapid destruction of the clot as soon as it is formed is typical of this type of purpura. Purpura itself needs definition; its name indicates a purplish discoloration, and usually this refers to the skin and perhaps the mucous membranes. In practice, the word "purpura" refers to the presence of well-defined ecchymoses, or petechiae, or both. The various types of purpura can sometimes be discriminated on clinical grounds alone. Thus, numerous regular petechiae, all of about the same size and associated with small ecchymoses, usually indicate the presence of thrombocytopenia. Petechiae that are vivid purple in color, irregular in size and shape, and found chiefly about the joints, are almost always pathognomonic of acute vascular (Henoch-Schönlein) purpura. Large areas of spreading ecchymoses with few or no petechiae are seen most commonly in disturbances of the clotting mechanism, as such hemophilia, but may also be seen in severe fibrinolysis.

Screening tests are becoming increasingly important for the study of a case presenting purpura, to establish which mechanism of the hemostatic process may be abnormal. Investigation can then be focussed on the phase of the process which appears deficient (19). Preliminary studies include, in our laboratory, tests for the evaluation of platelet function (platelet count, or, at least, the observation of the blood smear for platelets; clot retraction), platelet and vascular function combined (bleeding time, tourniquet test). The overall coagulation mechanism and the possibility of circulating anticoagulants are evaluated by means of the coagulation time, in glass or (with more sensitive procedure) in silicone-coated test tubes. Other tests frequently made, even if the clotting time is normal, include: prothrombin time of

serum (which evaluates the formation of thromboplastin): prothrombin time of plasma (which evaluates the conversion of prothrombin to thrombin); and plasma fibrinogen level. Observation of the clot for some time after completion of coagulation evaluates the presence or absence of fibrinolysis. If any of these tests gives abnormal results, thus indicating the insufficiency of any given phase of the hemostatic process, more analytical studies become necessary to establish the nature of the bleeding tendency. These studies include the visual observation of the capillary bed; investigation of the morphology and analytical investigation of single platelet constituents; determination of the concentration of the various coagulation factors, etc. The complete evaluation of the pathogenesis of a bleeding disorder is often a difficult procedure requiring not only a sound approach, but frequently an imaginative one.

THE THROMBOCYTOPENIC STATES

The platelets. This subject has undergone a striking development. As indicated in the large number of articles, the all-important role of platelets in the process of hemostasis can no longer be doubted. Platelets obviously play a mechanical role, by plugging areas where the continuity of the vessel has been interrupted. In addition, they represent a veritable chemical factory, producing or releasing a number of agents which are required to initiate or accelerate the various phases of the hemostatic process (5, 20). Serotonin, one of these agents, has been isolated from serum and identified as 5-hydroxytryptamine (21), at least in the ox if not in man (22). It has also been obtained synthetically as serotonin creatinine sulfate (23, 24). The origin of serotonin from platelets cannot be doubed since no serotonin is found in the serum obtained by the coagulation of platelet-free plasma (22). Its main physiologic effect consists in causing prolonged vasoconstriction following injury, thus favoring the process of blood coagulation (25). It is generally admitted that the function of platelets in clot retraction is mainly physical, these bodies representing foci of fibrin formation. Many years ago, however, Glanzmann postulated that platelets supplied an enzymatic factor responsible for the retraction of the clot (retractoenzyme) and Fonio (26) claims to have isolated such a factor from the platelet hyalomere. While the latter hypothesis is still doubtful, the importance of surface and the concentration of fibrinogen and thrombin (27, 28) in determining clot retraction have become more generally recognized. Platelet thromboplastic factor is an agent which combines with antihemophilic globulin to form thromboplastin, perhaps in stoichiometric proportions. A deficiency of this thromboplastic factor is responsible for the poor prothrombin consumption during clotting and thus the high prothrombin activity of serum typical of thrombocytopenic states. Platelet factor 1 accelerates the conversion of prothrombin to thrombin, and platelet factor 2, that of fibrinogen to fibrin. Platelet factor 3 or antiheparin factor (29) is probably identical with the thromboplastic factor (5). These various agents have been isolated from platelet preparations in a comparative-

ly pure form (5, 29) and their existence thus appears fairly certain. Finally, at least in the cow, platelets may contain antifibrinolysin (30).

"*Thrombocytoasthenias*."—The discovery of separate factors in platelets, each responsible for a specific role in the hemostatic process, has gone a long way to clarify the significance of "thrombasthenia" or "thrombocytoasthenia" (31). Under this name are now grouped a number of ill-defined hemorrhagic diseases characterized by: (*a*) bleeding, very seldom spontaneous and most often following trauma or surgical operation; (*b*) normal number of platelets many of which, however, present, at inspection of an ordinary smear, anomalies in size and shape (they are usually larger than normal and lack condensation of the chromomere). Since the appearance of platelets can vary greatly depending on the technic of collection, this evidence might be considered inadequate. Electron-microscope studies, however, have shown conclusively (32, 33) that platelets of thrombasthenic patients are morphologically abnormal. (*c*) Evidence of deficiency of one or more of the hemostatic functions in which platelets are known or thought to play a role. Positive tourniquet test, prolonged bleeding time, poor clot retraction, deficient prothrombin consumption during clotting, slightly prolonged plasma prothrombin time can be found in these patients, alone or in various combinations (31). The hemostatic defect can be corrected temporarily *in vivo* and *in vitro* by the administration of platelets (31). Reports on these hemostatic defects have appeared in the past few years, both in Europe and in this country (34, 35, 36). Two excellent reviews on the subject have been published by Quattrin (37) and Clavel (38). A recent report emphasizes that the bleeding tendency found in patients with chronic granulocytic leukemia and in some cases of myeloid metaplasia, where the platelet count may be high or at least normal, may be attributable to lack of serotonin in the platelets (39).

Idiopathic thrombocytopenic purpura (*ITP*).—Classification of the thrombocytopenic states is based firmly on the appearance of the bone marrow in regard to number and activity of megakaryocytes (40). Thus, thrombocytopenia may occur when the megakaryocytes in the marrow are reduced (amegakaryocytic type) or normal or increased (megakaryocytic type). Reduction of megakaryocytes may be attributable to bone marrow failure (aplastic or hypoplastic anemia), or to infiltration of the bone marrow by leukemic or neoplastic cells (leukemia, malignancies), or may be caused by nutritional deficiencies, as in pernicious anemia (41) or scurvy. Thrombocytopenia, in these cases, is the expression of failure of platelet production (amegakaryocytic or secondary thrombocytopenic purpura). In the idiopathic and hypersplenic types of thrombocytopenic purpura, on the contrary, the number of megakaryocytes is increased or, at least normal, and they present morphologic abnormalities which have been interpreted as evidence of reduced platelet production (42).

Important advances have been made in the understanding of the mechanism of idiopathic thrombocytopenic purpura (ITP) which have pointed out clearly that the disease is a syndrome with many varieties rather than a well

defined entity. Of particular importance is the need for distinguishing acute from chronic varieties of the disease (43). In the acute cases, which usually, but not always (44), appear after an infectious or viral (45) process or after exposure to chemicals or drugs, the disease is self-limited, and the course a matter of a few weeks to three or four months (44, 46). Bleeding from mucous membranes is striking at the beginning of the acute illness, and is attributable possibly to a blood vessel disturbance, in addition to the marked thrombocytopenia. Anticoagulants have been detected in the presence of infection (bacterial polysaccharides (47)). Splenectomy can be avoided by watchful waiting in at least seven of ten cases. The chronic cases have a very prolonged course, characterized by remissions and relapses. Bleeding from mucous membranes is unusual, except from such "injured" areas as the uterine mucosa, during catamenia, or following trauma. Thus, severe menorrhagia may be a symptom of ITP,[2] although it is often treated mechanically or by hormonotherapy without reference to such a possibility. Clinical and laboratory findings have been advocated for the differentiation of the acute from the chronic cases (48, 49, 50), including the observation that an abnormal $\alpha\chi$ globulin may be detected in the electrophoretic pattern of patients with acute ITP (51).

Experiments on platelet survival, conducted by injecting "viable" platelets in individual thrombocytopenic patients and following the time of their disappearance from the circulation, have demonstrated the presence of an extrinsic platelet destructive mechanism in practically all cases of ITP. In patients with amegakaryocytic thrombocytopenic purpura (aplastic anemia) the survival time of platelets is four to six days, provided these patients have never previously been transfused and do not present splenomegaly or circulating antiplatelet substances. These findings do not agree with those obtained by radioactive methods. Human platelets tagged with P^{32} have a very short survival time when injected in the circulation of patients with amegakaryocytic thrombocytopenia, being taken up rapidly by the spleen, liver, lungs, and other organs (52, 53). It appears that the failure of platelets to survive in these experiments is attributable to their loss of viability *in vivo*, consequent upon the excessive manipulations required for their separation and tagging. In ITP, on the other hand, platelet survival is considerably shorter: only a matter of a few hours in the acute variety, and of about 24 hr. in the chronic cases. Survival time is somewhat more prolonged in the hypersplenic type of thrombocytopenia (54, 55, 56). The mechanism or mechanisms causing the rapid destruction of injected platelets are not entirely clear. In the acute cases, allergic mechanisms within the tissues are probably at play, with the platelets and, perhaps, the megakaryocyte and the capillary wall as the shock organ (46, 48). In the chronic type, platelet agglutinating antibodies of auto-, iso- and "coating" type are demonstrable in at least 50 per cent of the cases (56 to 61). They may lyse (62, 63) as well as agglutinate platelets. Methods for their detection, their nature, and their mechanism of action have been published (58, 59, 60, 64). Platelet antibodies

probably produce thrombocytopenia by causing agglutination and, perhaps, lysis of circulating platelets, and by reducing the ability of the megakaryocyte to produce them (42, 60, 61). Whether their activity may be reduced by the administration of ACTH (adrenocorticotropin) or cortisone (61) is questionable. The mechanism of production of platelet agglutinins is not clearly understood. It is possible that bacteria, viruses (65), and other agents may modify platelets and make them antigenic to the host, i.e. "*auto-antigenic.*" In one instance, in which the nature of the platelet agglutinin was carefully studied (60) it showed all the features of an immune antibody. When a platelet agglutinin is present in high titer in the plasma of a patient with thrombocytopenic purpura, injection of the patient's plasma into a normal recipient induces thrombocytopenia of a few days' duration (66 to 69) accompanied, in especially marked instances, by clinical purpura (66). The thrombocytopenia, in this case, is more marked and more persistent than that resulting from the administration of normal plasma (70, 71). In both instances, however, the drop in platelet count can be demonstrated only if platelets are counted by indirect and not by direct methods (67, 71). The explanation of this finding is not clear. Platelet agglutinins and a significant thrombocytopenic effect can be observed only in some of the cases of idiopathic thrombocytopenic purpura, the incidence of these phenomena varying from 25 per cent (60) to 60 per cent (61) in two series of cases. Other factors may therefore be operative or our methods for detecting platelet antibodies may be relatively insensitive. A high titer of heterophile (Forssman's) antibody may be found in the serum of patients with ITP (72).

There can be no doubt that the last few years has witnessed a revolution in our thinking as to the pathogenesis of ITP. What seemed at one time to be a form of hypersplenism has now frequently become, as with acquired hemolytic anemia, an autoimmune disturbance. The immunologic concept of ITP, "immunothrombocytopenia," which was to a large extent initiated by Evans (57), has been very fruitful.

The role of the spleen in the disease is far from clear. It probably does not play any definite role in the acute variety, where it has been shown that spleen does not exercise any "selective" sequestration of platelets (73). This may occur, however, in other varieties of the disease (74). When platelet agglutinins are present, if is likely that the spleen removes platelets previously injured by platelet antibodies (58, 60, 61), a concept suggested by earlier experimental work (75). It has been concluded from these data that splenectomy may be particularly successful in patients whose plasma contains platelet agglutinations (61). This is not, however, substantiated by our experience. When the spleen is enlarged (*hypersplenic thrombocytopenia*) the effect of the spleen may be both local (sequestration of platelets) and humoral (inhibition of megakaryocytic activity). In most cases, the spleen then shows pathological changes such as Gaucher's disease, sarcoidosis, etc. (76). A factor inhibiting platelet delivery from the megakaryocytes ("thrombocytopen") may be found in the spleen, as well as in other tissues, and not

necessarily in higher amounts in the spleen of thrombocytopenic patients (77). An opposing factor ("thrombocytosin"), stimulating the production of platelets, has also been found in the spleen and other organs. This factor, a steroid, has been reported to have been used successfully in raising the platelet count and controlling the bleeding of patients with thrombocytopenic purpura (78). Since splenectomy, in these cases, is followed by explosive production and release of platelets from the megakaryocytes, there seems to be some evidence that a hyperfunctioning spleen may depress platelet production.

Progress in the understanding of thrombocytopenic states has unfortunately not been matched by comparable progress in therapy. The observation by Robson & Duthie (79) that ACTH and[2] cortisone improve markedly and rapidly the vascular resistance has represented an important advance in the management of thrombocytopenic states. These hormones, in comparatively high doses, are now used successfully in controlling and preventing the bleeding in thrombocytopenic patients, whether the thrombocytopenia is megakaryocytic or amegakaryocytic in type (80 to 87). Alone or in combination with platelet transfusions, ACTH and cortisone are very useful in tiding the patient over the initial bleeding crisis of acute idiopathic thrombocytopenic purpura and in controlling periodically the bleeding episodes of a patient of the disease who has failed to respond to splenectomy. These hormones are also usefully employed in the preparation of patients for splenectomy (88), since their use reduces bleeding at the time of operation. With one exception (89), most authors agree that the beneficial effect of ACTH and cortisone is attributable primarily to increased vascular resistance rather than to any effect on the platelet count. Thus, these hormones are relatively disappointing in their effect, as compared with the often striking results obtained in auto-immune hemolytic anemia. ACTH and cortisone may also reduce the bleeding time and have been used in the treatment of vascular pseudohemophilia (90). This is dubious and, in any case, requires a prolonged period of treatment. It is of interest that, on the contrary, the prolonged administration of ACTH or cortisone may induce bleeding typical of scurvy by depleting the body reserve of ascorbic acid (91).

Transfusion of platelets has now become a routine procedure in some institutions. Various methods for transfusion of platelets have been recently reviewed (92) and commented upon editorially (93, 94). Direct transfusion of polycythemic or normal blood (54, 55, 56), indirect transfusion of blood recently collected in entirely plastic or silicone-coated systems (92) appear to be the treatment of choice and within the realm of the practitioner. Technics have also been developed for the separation and concentration of platelets (95 to 99) since availability of nonwettable surfaces (100) and new anticoagulant technics (95) allow optimal separation of platelets without excessive damage. Differential centrifugation is the method of choice, although dextran (96) or PVP (97) may be used as sedimenting agents[3]. In general, platelet concentrates fail to survive normally when injected into individuals

with aplastic anemia, although they still exercise a fairly adequate but temporary effect on the hemostatic dysfunction and the bleeding tendency of these patients (54, 55, 56). Preservation of platelets achieved by Tullis (101) and by us (92) is still far from ideal, since such platelets quickly lose their viability. Indications for platelet transfusions include: (a) the control of bleeding in aplastic anemia and leukemia; (b) their use in ITP and thrombocytoasthemia to tide the patient over acute crises of bleeding; (c) the preparation of patients for splenectomy. Although the survival time of platelets in patients with ITP is minimal, their massive administration may control mucous membrane bleeding and often result in almost bloodless operations, as for splenectomy. Also, the use of platelet transfusions in amegakaryocytic thrombocytopenia, however, seems to present limitations, since some patients soon become resistant to them (55, 56, 102) in many cases as a result of the development of platelet antibodies (56, 102). Further work on this subject has brought out the finding that, in some cases at least, this is attributable to transfusion of platelets which are "incompatible." Four platelet groups (103) and a number of platelet types, varying from three (103) to eight (61), have been found; the former, by agglutination of platelets with plasma of normal individuals never previously transfused; the latter, by agglutination of platelets with the plasma of individuals who had received multiple platelet transfusions. The existence of platelet groups seems to receive confirmation from family studies, while the question of platelet subgroups or types is made exceedingly difficult by the fact that most of the patients whose plasma is used for typing have received transfusions from several different donors. It must be said that the entire subject of platelet groups and types is still in a state of preliminary knowledge and that, while platelets are certainly antigenic, studies of their grouping and typing are far from final. It is still a moot question whether, by giving perfectly compatible platelets, the development of iso-agglutinins may be prevented. In any case, this represents an important limitation to the use of repeated platelet transfusions (92) which, it is felt with reason (94), should be limited to patients where their use may be lifesaving, in preparation for splenectomy, and in severe bleeding crises.

Splenectomy remains the treatment of choice (104, 105, 106) in the chronic cases of the disease and in those acute cases that have become chronic (48). A detailed study of the mechanism of the beneficial effect of splenectomy was made by Robson (107), unfortunately prior to the recent observation on the importance of immunologic mechanisms. As mentioned above, splenectomy may induce a remission in the disease by a number of mechanisms: (a) by removing a "graveyard" for platelets injured by circulating agents (60, 61); (b) by removing the possible source of humoral factors causing inhibition of platelet production and delivery by the megakaryocytes (a classical view); (c) by removing a possible source of platelet autoantibodies (61, 103). The operation itself, in expert hands, has become of almost no consequence, especially since the introduction of ACTH and/or

cortisone and of platelet transfusions has greatly reduced the bleeding at operation. Technical aspects of splenectomy have been reviewed in a recent monograph (108). Unfortunately, it is impossible to predict in a given case whether a complete, partial, or no response will take place following splenectomy. Patients who have failed to respond to the operation remain a problem of management. Some of them, although their platelet count has failed to rise, experience but little bleeding (most often when suffering from intercurrent infections, etc.). Others continue to have a significant hemorrhagic tendency, and women may bleed considerably with their menstrual periods. ACTH and cortisone may be helpful in controlling hemorrhage in such cases. Accessory spleens are still considered by some as the cause for late relapse (109) but they are practically never found. Sites of accessory spleens to be looked for at operation are several, including the large omentum (110). Recently, Loeb *et al.* (111) tried to visualize accessory spleens in splenectomized patients with unmodified hemolytic anemia and idiopathic thrombocytopenic purpura by means of thorotrast. In a series of seven cases of idiopathic thrombocytopenic purpura, no successful visualization of an accessory spleen was possible.

Drug thrombocytopenic purpura.—This syndrome has received increasing attention in the past few years. Some drugs result in thrombocytopenia by direct injury of the bone marrow megakaryocyte. The number of these cells in the marrow becomes reduced, usually together with hypoplasia or aplasia of the erythroid and myeloid precursors as well. Drugs capable of inducing such a picture are many, and they all act probably by inhibiting enzymatic systems which are indispensable for the growth or maturation of the megakaryocytes, or by biologically competing with nutritional factors needed for the same purpose. Most myelosuppressive drugs may cause thrombocytopenia as one effect of their total action of the bone marrow. In general, the drop in the platelet count is an early sign of bone marrow injury, and platelets are the last element of the blood to return to normal in the recovery phase. A large number of drugs may exercise a similar effect: (phenantoin) (Mesantoin) (112); thiosemicarbazone (113); thyroid depressing drugs (114); radioactive gold (115); many coal-tar derivatives, some of which are extensively used in dermatology (116); antihistaminics (117); sulfonamides (118); arsenic (119); DDT (dichlorodiphenyltrichloroethane) (120, 121) and others. The presence of one or more nitro-benzene rings makes a compound, theoretically at least, capable of producing bone marrow injury (122, 123) and thus thrombocytopenia. Chloromycetin has recently received much attention as a potential cause of bone marrow damage (123 to 133). Although the evidence is largely circumstantial, it may be considered conclusive in some instances. There is a great variability in the individual response to such drugs, since at times minimal and even single doses of the drug may induce marked aplasia of the bone marrow and thrombocytopenia (132). A test capable of detecting *"in vitro"* which individuals may be expected to react unfavorably to this and other drugs would be of great value, but unfor-

tunately it is not yet available. At the same time, however, the cautious use of the drug in the initial phase of its administration may help to detect a blood reaction in time to prevent irreparable consequences. The use of medications only when clear cut indications for their use exist, and their discontinuance at the very moment any form of adverse reaction occurs, should help in reducing the incidence of bone marrow aplasia attributable to chloromycetin as well as to other related and unrelated drugs.

Sedormid [allylisopropylacetylurea (134)] quinidine (135 to 138), quinine (139), aminopyrin (140), or marbadal (140) may cause thrombocytopenia by an indirect or immunologic mechanism, which is closely associated with that found in some patients with ITP. The studies of Ackroyd on Sedormid purpura represent a classical contribution to the subject (141 to 144) and the investigations of the more recently studied quinidine thrombocytopenia have been more or less modeled on Ackroyd's concept. Certain individuals develop a factor of an antibody type in the plasma and the serum after the repeated or intermittent administration of the drug. When the drug is again given, even in small amounts, thrombocytopenia may develop as the result of agglutination and lysis of platelets in the presence of complement (141). The drug (partial antigen or hapten) is apparently needed to "couple" the agglutinating and/or lytic factor (antibody) to the platelet. Thus, if one observes such a patient for a period of time, one may find a platelet auto- and iso-agglutinin and a short survival time of injected platelets as long as the offending drug is present in plasma (145). Later, as the platelet count rises, the antibody can be detected only by the addition of the offending drug *in vitro*. The platelet agglutinating factor may persist in the patient's plasma from a few days to several years or even indefinitely (137, 146). In general, readministration of the drug is followed by another crisis of thrombocytopenia (147), but this rule has exceptions. Perhaps the routine use of *in vitro* tests may help to detect those patients developing hypersensitivity in whom long-term or intermittent administration of the drug is considered likely (145).

Neonatal thrombocytopenia.—There has been a revived interest in this subject. Thrombocytopenia at birth may be symptomatic of congenital syphilis, sepsis, congenital leukemia (148); may represent one of the symptoms of Fanconi's syndrome of hypoplastic anemia with multiple congenital defects (when this is present at birth), or may accompany severe cases of erythroblastosis fetalis. In rare cases, megakaryocytes may be congenitally absent or greatly decreased (149). This may represent a variety of the Fanconi's syndrome, since other congenital abnormalities are often present.

Of greater importance and certainly more frequent is a picture of thrombocytopenia with all the characteristics of idiopathic thrombocytopenic purpura. The literature on the subject has been reviewed by Robson (150) and by Epstein, Lozner *et al.* (151). Cases of neonatal thrombocytopenia belonging to this group may be divided into two varieties: those occurring in the new-born of thrombocytopenic mothers and those in the new-born of non-

thrombocytopenic mothers (150, 151). The mechanisms leading to thrombocytopenia are probably as numerous as those found in ITP itself. As Epstein, Lozner *et al.* (151) have suggested, the passage of antiplatelet substances from the maternal to the fetal circulation may cause thrombocytopenia. This is now a distinct possibility in view of the demonstration of platelet agglutinins in cases of chronic idiopathic thrombocytopenic purpura. There is general agreement that splenectomy should be done in mothers with idiopathic thrombocytopenic purpura (151), preferably prior to the fifth month of pregnancy, since this reduces the incidence and severity of the purpura in the newborn. In another, perhaps more unusual group of cases, the thrombocytopenia of the newborn may be attributable to platelet group or type incompatibility between mother and fetus (61), corresponding to the far more common red blood cell group incompatibilities. Neonatal thrombocytopenia is usually self-limited (150, 151).

Combinations of thrombocytopenic purpura with hemolytic anemia, including thrombohemolytic (thrombotic) thrombocytopenic purpura.—Evans pointed out cases in which there was both acquired hemolytic anemia ("immunohemolytic anemia") and ITP ("immunothrombocytopenia"). He pointed to many fundamental similarities between these two syndromes, affecting as they did different cell types. "Evans Syndrome," in which there is both auto-immune hemolytic anemia with a positive Coombs' test and ITP, has been seen with increasing frequency. Another, perhaps even more common, disorder is one in which at least three cell systems are involved: the red cell, the platelet, and the endothelial lining of small blood vessels. This has been called variously, the most commonly used name being that applied by Singer, i.e. "thrombotic thrombocytopenic purpura." This term, although alliterative, does not include the important hemolytic component of the disease. With increasing awareness of this syndrome, more and more cases are being diagnosed prior to necropsy. The triad of thrombocytopenia, hemolytic anemia, and transient and changing neurologic symptoms (chiefly cerebral) is now well recognized. In addition, the disease is now known to present various combinations of these symptoms. Singer's descriptions of the disease remain authoritative ones (152, 153). Gendel *et al.* (154) have attracted attention to the existence of chronic varieties of the disease, and the possibility exists that splenectomy might in these cases induce a temporary, but prolonged, remission (155). No red cell or platelet antibodies have been, thus far, demonstrated in the plasma of the patients, although in one case, a heterophile antibody against platelets was found (156). The significance of this finding is not clear. Despite the negative immunologic findings, there is a striking shortening of both red cell and platelet survival, thus indicating the presence of some form of extrinsic destructive factor, possibly immunologic. Thrombi of small blood vessels are found primarily in the heart muscle, brain, and adrenal gland and involve capillaries and precapillaries (157). Skin and muscle biopsies in these cases are usually negative and even when the spleen is available for inspection, a careful and prolonged search may be

necessary before the typical lesions are detected. At least in two cases, a diagnosis could be made by the demonstration of thrombotic blood vessels in bone marrow sections (158). It is uncertain whether the hyaline thrombi found in this disease represent in fact platelet thrombi, or whether they are primarily attributable to blood vessel lesions, related histologically to periarteritis (159). The latter opinion appears to be prevailing. Orbison (14) finds aneurysmal dilatations of the vessels to be a rather specific finding in the disease. In certain cases of apparently typical auto-immune hemolytic anemia or ITP, in which the therapeutic response to steroid hormones or to splenectomy has been minimal if at all, the eventual course proves the presence of thrombohemolytic disease.

Idiopathic thrombocytopenic purpura in other fundamental diseases.—It is becoming increasingly apparent that even in what appears to be classical "idiopathic" thrombocytopenic purpura, a more important fundamental disease may be present (76). Prominent amongst these, and at times revealed only by splenectomy, are such conditions as disseminated lupus (160), tuberculosis (161), sarcoidosis (162, 163, 164), lymphosarcoma, and lymphocytic leukemia. As we have stated repeatedly, it is therefore important, when confronted with ITP or hemolytic anemia or both, to remember that these may be merely symptomatic of "above the surface" indicators of a larger, much more important area of "iceberg," i.e. a fundamental disease "below" the surface (49). Disseminated lupus, with its diverse manifestations (thrombocytopenia, leukopenia, hemolytic anemia, arthritis, angiitis) appears to be the multi-immunologic disorder *par excellence* and should always be suspected in ITP particularly if any somewhat atypical features are present.

ACUTE VASCULAR PURPURA

Acute vascular, or Henoch-Schönlein purpura, which is not simply a disorder of the skin blood vessels, but of small blood vessels generally, is beginning to assume a logical place among the hyperimmune or immuno-allergic disorders (165). Almost always it follows an acute infection, usually tonsillitis, streptococcus sore throat, and the like (46). It may be associated with pulmonary tuberculosis (166). There is a period of one to three weeks between the end of the infection and the beginning of the purpura, which we have named "the build-up period," and which is followed by an "explosive" outbreak of severe skin purpura, arthralgia or actual arthritis with purpuric lesions about the joints, severe intestinal cramps often accompanied by bleeding (simulating at times surgical emergencies (167)), gross hematuria (with the manifestations of acute glandular nephritis), and at times other disturbances, including pleurisy. Clark & Jacobs (12) produced experimental vascular purpura in dogs by the use of a hetero-immune antiblood vessel serum. The blood vessel lesions resembled closely those found in Henoch-Schönlein purpura. These authors referred to a hitherto neglected series of studies by Japanese investigators who had produced all the various lesions of Henoch-Schönlein purpura in guinea pigs by the use of hetero-immune sera. From

these various observations, there appears to be little doubt that acute vascular purpura is an immunologic disorder affecting small blood vessels throughout the body. In this respect it may be related to periarteritis nodosa. Indeed, the suggestion has been made (168) that periarteritis nodosa and acute vascular purpura "constitute the same condition, and that whether the arteries or capillaries are involved depends on variations in the conditions of pathogenesis operating in any particular case." Therapy with ACTH or cortisone, as in other hyperimmune disorders, may cause rapid and striking improvement of all the various disturbances (169) except for the renal one, which often goes on to chronic intractable nephritis.

COAGULATION DEFECTS

New tests for coagulation defects, newly discovered coagulation factors, and some recently identified clinical entities have been described during the past few years. To a certain extent, progress has derived from the progressively greater use of relatively pure agents in the *in vitro* work. As always, however, the most significant advances in the field have come from the analytical study of the bleeding patient.

A group of new laboratory tests has been introduced. Some of them are directed to the evaluation of single factors of the blood coagulation process, some to the overall sufficiency of any individual phase of this mechanism. The "thrombin generation test" (170, 171) and the "thromboplastin generation test" (172) have proven valuable tools in the investigation of the interaction of various of the coagulation factors. The latter method, especially, seems to represent a very versatile procedure in the investigation of the formation of thromboplastin and in the quantitative determination of the various agents which take part in it. Analytical tests for the determination of antihemophilic factor concentration (173, 174) have come to the fore in view of the recent developments in the field of the hemophilia syndrome. The "thromboplastinogen activation test" (175, 176) distinguishes between the defect of prothrombin conversion during clotting attributable to deficiency of antihemophilic globulin and that attributable to platelet defect. Unfortunately, however, it does not reveal finer deficiencies of the plasmatic part of the formation of thromboplastin. Other technics introduced in recent months include procedures for the determination of the clotting time by photoelectric methods (177), of the circulating thrombin (178), prothrombin (179 to 183), stable factor (184, 185), and a modification of a method for the determination of the labile factor (186). Technical procedures for the study of blood coagulation are reviewed by Mann (187). "Coagulogram" is the definition proposed for the series of tests which are required to classify a hemorrhagic disorder (188, 189).

The theory of the mechanism of the coagulation of blood remains confusing. There have been recent reviews to which the reader is referred (190, 191) including an historical presentation by Milstone (192). Clotting of fibrinogen is discussed by Laki (193). The major confusion remains in that

phase of the coagulation process leading to the conversion of prothrombin to thrombin. In addition to calcium and thromboplastin two other factors are required: labile factor (plasma Ac-globulin, proaccelerin, factor V) and stable factor (proconvertin, factor VI, factor VII, SPCA precursor). The necessity for a unification of nomenclature has been met in a number of reviews (5, 194, 195). "Stable factor," a fairly recent addition to the family of coagulation agents, has been discussed in several articles (185, 196 to 200). The individuality of these two coagulation factors has received further support from their separation by electrophoretic (201) and chemical (202) procedures and the discovery of several cases of congenital deficiency of labile (203, 204, 205, 206, 207, 208, 209) and stable factor (5, 197, 208, 210, 211). It is still disputed whether a precursor of the stable factor is present in plasma which becomes activated in serum. Words of caution have been raised by many against the undue multiplication of new agents. In has been pointed out that some of the accessory factors described are, in reality, a mixture of stable and labile factor or, more commonly, of stable factor and prothrombin. An entirely new concept has also arisen from the work in two laboratories. Plasma thromboplastin, the final product in the first intermediary step of coagulation of blood has been isolated in a state of considerable purity (212), and a series of combinations of various factors during the conversion of prothrombin to thrombin have been analyzed (213). These findings suggest that an hypothetical new agent may, in reality, represent only an intermediate step or factor in the process of blood coagulation.

The prothrombin consumption test continues to be, simultaneously, the subject of attack and the instrument of numerous advances in the field. It is generally agreed that its pathologic variations represent a fairly good, although only roughly quantitative, index of disorders in the first phase of the coagulation process, i.e. the formation of thromboplastin. In the past two years, this test has been largely instrumental in the discovery of accessory factors in the formation of thromboplastin, and in causing a complete re-evaluation of the subject of hemophilia.

Until very recently, deficiency of antihemophilic globulin and of platelet thromboplastin factor were considered to be the only possible causes of an abnormal prothrombin consumption during clotting. Thus, if the platelets were qualitatively and quantitatively normal, a poor consumption of prothrombin during clotting was considered pathognomonic of hemophilia. This could be considered a complacent attitude since many unexplainable anomalies would often be found in the study of a patient with hemophilia. Thus, a normal yield of antihemophilic globulin had been obtained from plasma of severe "hemophiliacs" (214); and the mixture of plasmas from two known hemophiliacs had been found to present, at times, a normal clotting time (215) and normal prothrombin consumption (216). It had been noted that the hemostatic mechanism of known "hemophiliacs" could be normalized at times by the administration of stored plasma, which contains practically no antihemophilic globulin, or, in reverse, could fail to respond

to the administration of purified antihemophilic globulin (217). An answer to these problems has come from a number of investigations (218, 219, 220). From these has come the conclusion that, in addition to the platelet thromboplastic factor and antihemophilic globulin, at least one, and perhaps two or more, plasmatic factors are necessary for the formation of thromboplastin. One of these factors, plasma thromboplastin component (PTC), has been well characterized and is readily separable from antihemophilic globulin (221). Its deficiency, variously described as Christmas disease (220, 222), Kincaid anomaly (221), hemophilia B (223), produces a clinical picture which is indistinguishable from hemophilia, even from the genetic standpoint. Simple tests have been evolved for the laboratory discrimination between hemophilia and PTC deficiency[2] (221) based on the fact that PTC can be absorbed from oxalated plasma and is present in serum, while antihemophilic globulin is not.

Another plasma thromboplastic factor, plasma thromboplastin antecedent (PTA) has been described (224). It is not clear at the present time whether it represents a new coagulation factor or an intermediate step in the process of formation of thromboplastin. This factor appears to have properties of both antihemophilic globulin and of PTC. Plasma rich in PTA can correct both hemophilic and PTC-deficient plasma[2]. The role of PTC and PTA in the formation of thromboplastin is not clear. Both may act as accelerators of the reaction between platelet thromboplastin factor and antihemophilic globulin. PTC and PTA were postulated as the result of the study of the utilization of prothrombin during clotting of mixtures of various plasmas all presenting the same clotting anomaly. It has been intimated that, by the use of this technic, a fourth plasma thromboplastic component may exist. In fact, in our experience, several new factors could conceivably be postulated, on the basis of work on the reciprocal correction of mixtures of plasmas which present a poor prothrombin consumption. The method used, however, is not without criticism and the existence of new plasma thromboplastic factors should perhaps be recognized only after extensive characterization such as that carried out by Aggeler *et al.* (221) and Schulman & Smith (218) for PTC.

With regard to the incidence of hemophilia, PTC-deficiency, and PTA-deficiency there is evidence that about one case in five with apparently typical hemophilia represents PTC deficiency (225). The incidence of PTA deficiency is given as fairly high by Rosenthal who also points out that this hemorrhagic disease includes mostly cases of moderate thromboplastic deficiency, with normal or only slightly prolonged clotting time, and is transmitted as a dominant characteristic. Other important advances in the field of hemophilia have been concerned with the hereditary aspects of the disease. Authentic cases of hemophilia in the female have been described (226, 227, 228). Such an eventuality may seem attributable to gene mutation or to the mating of a hemophilic male with a carrier female. This combination is said by many of the older observers to be lethal. It might not be so if the

father suffers only from a mild form of the disease. A great deal of attention has been given to the discovery of the hemophilia-carrier female. Various observers have emphasized the presence of mild coagulation defects in females of the families of known hemophiliacs (229). Owren (230) has found a slow activation of proconvertin to convertin (stable factor precursor to stable factor) in females of hemophilic families. It has also been observed that the plasma of known or suspected hemophilia carriers does not completely correct the prothrombin utilization defect of known hemophilic plasma (231), thus presumably indicating a minor deficiency of antihemophilic globulin. These carriers also present an anomaly of their plasma electrophoretic pattern (presence of $\alpha\chi$globulin) which is characteristically found in patients with hypothromboplastinemias (hemophilia, PTC-, PTA- deficiencies). By the use of delicate tests for the detection of minor deficiency in the concentration of antihemophilic globulin, Graham *et al.* (232) have recognized many cases of hemophilia that would otherwise have gone undetected. These authors have concluded from genetic studies that mild hemophilia is linked to a gene which is allelomorphic to the classical hemophilia gene. The gene (h[m]) would also be transmitted as a sex linked recessive characteristic. It is quite possible that various degrees of antihemophilic globulin deficiency may be attributable to the presence of different genes. This would explain the often puzzling finding of a fixed degree of severity of the disease in a hemophiliac family. Cyclical variations in the severity of bleeding in hemophilia have been known for a long time. It is thought that a drop in prothrombin and labile factor concentration may directly precede the occurrence of bleeding (233).

The question of nomenclature for the hemorrhagic states resulting from deficiency of thromboplastic formation has recently arisen. There is no doubt that the definition of hemophilia (for the disease characterized by deficiency of antihemophilic globulin) and hemophilia-like disease (for the disease attributable to the presence of a circulating anticoagulant capable of inhibiting the formation of thromboplastin) is firmly entrenched in the literature. The designation of hemophilia B and C for PTC deficiency respectively has been recommended by various authors. At first glance the latter system of nomenclature seems to offer several advantages: it leaves ample room for the definition of hemorrhagic disorders belonging to the same group and to be, very likely, recognized in the future; it is also sufficiently noncommittal with regard to the definite role of the various coagulation agents missing in the clotting process. Finally, it stresses the common feature of all disorders of this group: the deficient formation of thromboplastin. It is necessary to point out, however, that a major objection to this classification is represented by the fact that there is no genetic relationship of any kind among antihemophilic globulin, PTC and PTA (234, 235). Perhaps hemophiloid state A, B, etc. (234) or hemophilia-like state A, B, etc. (235) might be more acceptable.

Very little advance has been seen in the therapy of hemophilia and re-

lated states. Use of "fresh" plasma or blood is still imperative in the treatment of bleeding episodes in hemophilia. Heparinized plasma may have greater and more prolonged corrective effect (236). Fresh blood or plasma is also effective in the treatment of PTC and PTA deficiency where, however, one can also use stored blood and plasma or serum. By this method of treatment, one obtains protection lasting from 24 to 68 hr. to 6 to 10 days in hemophilia, and about seven days in PTC and PTA deficiency respectively. Antihemophilic globulin is found in Fraction I of Cohn, together with fibrinogen, and salt impurities. Fibrinogen, infectious hepatitis virus, and homologous serum jaundice virus are also concentrated in this fraction. This may explain the somewhat high incidence of these complications in hemophiliacs who are transfused repeatedly with these preparations. Rapidly frozen and lyophilized, freshly collected plasma are also useful in the treatment of hemophilia. ACTH and cortisone may be of help in the management of acute bleeding. These hormones have a complex, although controversial, effect on the clotting mechanisms and their therapeutic effect in hemophilia, if any, is attributable primarily to the increased vascular resistance induced by the drug. Splenectomy has been advised in the treatment of hemophilia (237), but such a radical method requires much deliberation before it is even considered. Organic di-iodo compounds have been claimed to control hemophilic bleeding (238).

Intra-articular injection of hyaluronidase has been reported successful in the relief of pain and swelling of hemophilic hemarthroses (238a). As much blood as possible is aspirated and then 150 to 1,500 TRU (turbidity reducing units) of the enzyme in 1 per cent procaine are injected. An elastic bandage is applied and the patient encouraged to begin active motion of the joint. Repeated injections may be necessary. Best results are obtained in fresh hemarthroses, occasionally in older ones (4 to 6 weeks). The enzyme apparently facilitates reabsorption of blood through increased synovial permeability. It is extremely important to remember that the hemostatic mechanism of these patients should be normalized with transfusions of fresh, frozen, or lyophilized plasma before the enzyme is injected into the joint, to avoid severe peri- and intra-articular bleeding.

Afibrinogenemia is a rare hemorrhagic disorder with great theoretical interest. A case has been described by Lawson (239) showing that menstrual periods are normal in those patients, a fact not available from previous literature. Other cases have also been reported (240, 241, 242). A careful analysis of the coagulation mechanism based on the study of three such cases has been made by Alexander et al. (243). The results obtained have proven, as suspected, that fibrin does not play any definite role in the autocatalytic phase of blood coagulation. By the use of an immunochemical method (244), Gitlin & Borges (245) have been able to show that, in patients with afibrinogenemia, the survival rate of the protein is 5 to 6 days, thus confirming earlier findings obtained with radioactive technics (246). Hypofibrinogenemia is also, at least in part, responsible for the bleeding tendency in poly-

cythemia vera and secondary polycythemia of heart disease (247, 248). We believe that the hypofibrinogenemia in these states may be attributable to the excess utilization of this protein for the increased erythropoietic activity (249). While the hypofibrinogenemia of polycythemic states most often only causes moderate skin bleeding, it may greatly complicate bleeding from peptic ulcer (a common feature in polycythemia vera). Also, polycythemic patients are potentially very dangerous bleeders in the course of operative procedures. This has been particularly emphasized in the course of cardiac surgery in congenital heart disease with polycythemia and cyanosis. Hypoprothrombinemia may also be found in these patients (247). A satisfactory method, which we have found especially useful in preparing such patients for operation, consists in bleeding them repeatedly until their hematocrit value is within normal value, and transfusing back normal plasma in a volume equal to that withdrawn.

Perhaps the most fascinating aspect of coagulation defects is represented by advances in the knowledge of hemorrhagic diseases which are, perhaps, rare but still of great importance from the standpoint of management. These are the hemorrhagic disorders attributable to circulating anticoagulants. Physiologic anticoagulant mechanisms include antithromboplastins, antithrombin, and a number of protein interactions and absorption phenomena. A new antithrombin reaction has been described (250) in the dog. It is believed by some that excess antithromboplastic (anticephalin) may be the most important or, at least, one of the significant mechanisms leading to the coagulation defect in hemophilia (251). Transfusion of hemophilic blood, however, fails to induce abnormality of the clotting mechanism (252), even when collected and administered with entirely nonwettable systems (253). Idiopathic hyperheparinemia has been reported (254). In addition, three main groups of circulating anticoagulants have been described (255). One is attributable to the presence of abnormal proteins in association with multiple myeloma, collagen diseases and, as described by Waldenström, as macroglobulinemia (256, 257). In these instances, the abnormal protein interferes with the normal clotting mechanism, particularly with the fibrogen→fibrin reaction. Another type of anticoagulant is one which interferes with the "activity" of thromboplastin. Two such instances have been reported by Conley and Hartmann in lupus erythematosus (258). Finally, the best known type of anticoagulant is one which inhibits the "formation" of thromboplastin. This type of anticoagulant has been found in many conditions including the collagen diseases (259), following drug hypersensitivity (penicillin) in subacute bacterial endocarditis with cryoglobulinemia (260), and in hemophiliacs receiving multiple transfusions or multiple injections of purified antihemophilic globulin (261 to 264). The last instance represents a very important therapeutic problem. The use of a large amount of fresh plasma may allow control of bleeding (264); limitation of blood transfusions (262) and use of ACTH and cortisone (264) may reduce the titer of the anticoagulant and help the control of bleeding. It is interesting that many of the

hemophiliacs who have been found to develop an anticoagulant, have also been found to be $D^{11}(-)$ individuals receiving $D^u(+)$ blood. Of great theoretical importance is the development of anticoagulants during pregnancy. These may reach a high titer during pregnancy and disappear some time after delivery. In one case at least, the anticoagulant passed into the fetal circulation and was present in the child's circulation for some time after birth (265). In some cases, Rh incompatibility was also present between mother and fetus, emphasizing that, perhaps, an antigen-antibody mechanism was at the basis of their formation. Recovery may follow some time after delivery (265). In occasional cases, no presumptive explanation can be offered for the development of the anticoagulant (266).

FIBRINOLYTIC MECHANISMS, FIBRINOLYTIC PURPURA AND RELATED STATES

The new interest in the fibrinolytic mechanism lies equally in its importance as a potential factor in the control of intravascular clotting, as well as in its role in the pathogenesis of severe bleeding tendency. "Purpura thrombolytica" (267) or "fibrinolytic purpura" (268) are convenient, although incomplete, definitions for this bleeding tendency, since skin hemorrhage is only a minor aspect of the hemorrhagic disorder. Internal bleeding is more frequent and severe. A good review of fibrinolytic states is offered by Favre-Gilly *et al.* (269).

It is generally agreed today that profibrinolysin (an inert precursor) is converted to active fibrinolysin by either tissue kinases or bacterial products (streptokinase, staphylokinase, etc.) (268). It is disputed whether bacterial activators either act directly on profibrinolysin or through the activation of a prokinase (270). Inhibitors (antikinase, antifibrinolysin) are also present. Like the blood coagulation system, the fibrinolytic system is a very unstable mechanism, the equilibrium of which can easily be upset by a number of causes. Activation of fibrinolysin causes destruction of the formed clot only and, if activation is massive, of other coagulation factors as well. Severe bleeding follows. Activation of fibrinolysin is seen in a number of conditions, such as thoracic surgery (271) and uterine surgery (272). Lung and uterine tissue are particularly rich in kinases. Excessive fibrinolysis is a not infrequent finding in extensive intravascular clotting, in the course of shock (272), extensive burns, transfusion reactions (273), some cases of cirrhosis of the liver, leukemia, radiation injury, in the course of pancreatic surgery (274), and in obstetrical accidents resulting from Rh incompatibility. In special instances, the lytic mechanism has been found to be attributable to the presence in the circulation of proteolytic enzymes, perhaps differing from fibrinolysin. This is the case in prostatic carcinoma with widespread dissemination (275, 276, 277). Under these circumstances a preformed proteolytic enzyme may enter the circulation and, if in sufficient amount, may cause destruction of fibrin and fibrinogen as well as other coagulation factors (5, 277).

A special problem is presented by obstetrical accidents in which severe, generalized bleeding follows miscarriages (especially if criminally induced),

intra-uterine death of the fetus attributable to various causes but most commonly to Rh incompatibility between mother and fetus (278, 279, 280), premature separation of placenta, etc. The bleeding is undoubtedly attributable to severe hypofibrinogenemia and perhaps to the appearance of a powerful antithrombic anticoagulant in the circulation (281, 282, 283). Hypofibrinogenemia may result from one of two mechanisms. The penetration of amniotic parts and/or tissues into the circulation of the patient may cause (these tissues being thromboplastic in nature) intravascular clotting and consequent defibrination (282, 284, 285, 286). On the other hand, amniotic parts and tissues also contain kinases and may cause activation of fibrinolysin with destruction of fibrinogen and of fibrin (281, 287, 288). There is good clinical and experimental evidence for both mechanisms. Perhaps they may even be present simultaneously in the same case (286) since it is known that intravascular clotting is followed by activation of fibrinolysin. It is often therapeutically important to know the basic mechanism of the hypofibrinogenemia in the individual case of bleeding. This search should always include the study of the ability of the patient's plasma or serum to lyse a normal clot. This test is preferable to the simple observation of the clotted blood since the clot may sink to the bottom and appear lysed when, as in polycythemia, the fibrinogen content is low and perhaps, as in polycythemia and in shock, the cellular mass is increased. Finally, some cases of severe hypofibrinogenemia may be attributable to extreme liver failure, the liver being unable to produce the protein (289).

Control of bleeding resulting from hypofibrinogenemia and fibrinolysin is a complex task which requires different handling from case to case. ACTH and, to lesser extent, cortisone decrease the fibrinolytic activity of plasma by elevating the antifibrinolysin level (290). These have proved of real value in cases like disseminated prostatic carcinoma, where the output of the lytic agent into the circulation continues, and, until other therapeutic procedures such as stilbestrol administration or orchidectomy, may reduce the extent of the metastases (277). The use of soya bean inhibitor has also been advocated in such cases (275). In most obstetrical and operative accidents purified fibrinogen is of great value. This is also the case for all other conditions in which the activation of fibrinolysin is a temporary feature. In cases of placenta previa, the combination of fibrinogen administration, and perhaps ACTH and cortisone, has definitely reduced the number of cases where death follows uncontrollable bleeding. Emptying of the uterus, or prompt delivery as soon as bleeding is noticed, appears necessary. In some cases, hysterectomy may become necessary to save the patient's life. The literature gives a definite impression that prevention of shock is very important if any therapeutic measure is to be successful in these cases, thus advising the liberal use of whole blood and plasma. The therapy of a case of severe fibrinolysis occurring during the puerperium is an emergency requiring almost full time management.

LITERATURE CITED[a]

1. Burstein, M., *La Coagulation du Sang* (Masson & Cie Publ. Paris, France, 172 pp., 1949)
2. Quick, A. J., *Physiology and Pathology of Hematosis* (Lea & Febiger Publ. Philadelphia, Penn., 1951)
3. Biggs, R. and Macfarlane, R. G., *Human Blood Coagulation and its Disorders* (Blackwell Publ., Oxford, England, 406 pp., 1953)
4. Seegers, W. H., *Harvey Lectures Series* **47,** 180 (1952–1953)
5. Stefanini, M., *Am. J. Med.*, **14,** 64 (1953)
6. Owren, P. A., *Am. J. Med.*, **14,** 201 (1953)
7. Quick, A. J., *Am. J. Med.*, **14,** 349 (1953)
8. Lozner, E. L., *Am. J. Med.*, **14,** 459 (1953)
9. Ackroyd, J. F., *Am. J. Med.*, **14,** 605 (1953)
10. Roskam, J., *L'hémostase spontanée* (Masson & Cie Publ. Paris, France, 280 pp., 1951)
11. Spaet, T. H., *Blood*, **7,** 641 (1952),
12. Clark, W. G., and Jacobs, E., *Blood*, **5,** 320 (1950)
13. Humble, J. A., *Blood*, **4,** 69 (1949)
14. Orisbon, J. C., *Am. J. Pathol.*, **28,** 129 (1952)
15. Chambers, R., and Zweifach, W. B., *Physiol. Rev.*, **27,** 436 (1947)
16. Zweifach, W. B., Chambers, R., Lee, R. E., and Hyman, C., Jr., *Ann. N. Y. Acad. Sci.*, **49,** 553 (1948)
17. Chambers, R., and Zweifach, W. B., *Factors Regulating Blood Pressure, Trans. 3rd Conf.* (Josiah Macy, Jr., Foundation, New York, N. Y. 280 pp.)
18. Lutz, B. R., *Physiol. Rev.*, **31,** 107 (1951)
19. Stefanini, M., *Bull. New Engl. Med. Center*, **12,** 102 (1950)
20. Paulssen, M. M. P., *Stollingsfactoren Aanwezig in Thrombocyten* (Scheltema f. Holkema's Boekhandel en Uitgeversmaatschappij, N. V., Amsterdam, Holland, 179 pp., 1951)
21. Rapport, M., Green, A., and Page, J., *Science*, **108,** 329 (1948)
22. Bracco, M., and Curti, P. C., *Haematologica*, **7,** 721, (1953)
23. Hamlin, K., and Fische, F., *J. Am. Chem. Soc.*, **73,** 5007 (1951)
24. Speeter, M., Heinzelmann, R., and Weisblat, D., *J. Am. Chem. Soc.*, **73,** 5514 (1951)
25. Zucker, M. B., *Am. J. Physiol.*, **148,** 275 (1947)
26. Fonio, A., *Acta Haematol.*, **8,** 352 (1952)
27. Butz-Olsen, O. E., *Clot retraction* (Chas. Thomas Publ., Springfield, Ill., 149 pp., 1952)
28. Quick, A. J., and Hussey, C. V., *Science*, **112,** 558 (1950)
29. Van Creveld, S., and Paulssen, M. M. P., *Lancet*, **II,** 242 (1951)
30. Johnson, S. A., and Schneider, C. L., *Science*, **117,** 229 (1953)
31. Stefanini, M., Salomon, L., and Perez, S. E., *Am. J. Med.*, **14,** 529 (1953)
32. Glanzmann, E., *Ann. Paediat.*, **178,** 349 (1952)
33. Braunsteiner, H., *Klin Wochschr.*, **29,** 335 (1951)

[a] This list includes only monographs or articles which could be examined in the original by the reviewers. With few exceptions, the bibliography includes only contributions published after January 1, 1951.

34. Sussman, L. N., Wald, N., and Rosenthal, R. L., *Blood*, **7**, 1100 (1952)
35. de Vries, A., Shafrir, E., Efrati, P., and Shamir, Z., *Blood*, **8**, 1000 (1953)
36. Jurgens, R., and Forsius, H., *Schweiz. med. Wochschr.*, **81**, 1268 (1951)
37. Quattrin, N., *Le Diatesi Emorragiche Thrombopatiche* (Ediz. Minerva Medica, Turin, Italy, 245 pp., 1950)
38. Clavel, R., *Dysmorphies Plaquettaires Hemorrhagiques et Constitutionelles* (Camille Annequin, Publ., Lyon, France, 128 pp., 1950)
39. Bigelow, F. S., *J. Clin. Invest.*, **32**, 555 (1953)
40. Presley, S. J., Best, W. R., and Limarzi, L. R., *J. Lab. Clin. Med.*, **40**, 503 (1952)
41. Kissmeyer-Nielsen, F., *Acta Med. Scand.*, **141**, 125 (1951)
42. Pisciotta, A. V., Stefanini, M., and Dameshek, W., *Blood*, **8**, 703 (1953)
43. Hirsch, E. O., and Dameshek, W., *Arch. Internal Med.*, **88**, 701 (1951)
44. Newton, W. A., and Zuelzer, W. W., *New Engl. J. Med.*, **245**, 879 (1951)
45. Fisher, O. D., and Kraszewski, T. M., *Arch. Disease Childhood*, **27**, 144 (1952)
46. Clement, D. H., and Diamond, L. K., *Am. J. Diseases Children*, **85**, 259 (1953)
47. Freeman, G., *Blood*, **7**, 234 (1952)
48. Stefanini, M., and Dameshek, W., *Lancet*, **II**, 209 (1953)
49. Dameshek, W., and Stefanini, M., *Med. Clin. N. Amer.*, **1395** (1953)
50. Stefanini, M., Dameshek, W., and Bernfeld, P., *Clin. Research Proc.*, **1**, 69 (1953)
51. Bernfeld, P., and Stefanini, M., *Proc. Soc. Exptl. Biol. Med.*, **77**, 551 (1951)
52. Julliard, J., *et al.*, *Presse Méd*, **60**, 518 (1952)
53. Mueller, J. F., *Proc. Soc. Exp. Biol. Med.*, **83**, 557 (1953)
54. Stefanini, M., Chatterjea, J. B., Dameshek, W., Zannos, L., and Perez, S. E., *Blood*, **7**, 53 (1952)
55. Hirsch, E. O., and Gardner, F. H., *J. Lab. Clin. Med.*, **39**, 556 (1952)
56. Sprague, C. C., Harrington, W. J., Lange, R. D., and Shapleigh, J. B., *J. Am. Med. Assoc.*, **150**, 1193 (1952)
57. Evans, R. S., Takahashi, K., Duane, R. T., Payne, R., and Liu, C., *Arch.Internal Med.*, **87**, 48 (1951)
58. Miescher, P., Vannotti, A., Cruchaud, S., and Hemmeler, G., *Exptl. Med. and Surg.* **10**, 265 (1952)
59. Dausset, J., Delafontaine, P., and Fleuriot, Y., *Sang*, **23**, 373 (1952)
60. Stefanini, M., Dameshek, W., Chatterjea, J. B., Adelson, E., and Mednicoff, I. B., *Blood*, **8**, 26 (1953)
61. Harrington, W. J., Sprague, C. C., Minnich, V., Moore, C. V., Ahlvin, R. C., and Dubach, R., *Ann. Internal Med.*, **38**, 433 (1953)
62. Ninni, M., *Haematologica*, **36**, 693 (1952)
63. Tullis, J. L., *New Engl. J. Med.*, **249**, 591 (1953)
64. Stefanini, M., and Silverberg, J. H., *Am. J. Clin. Pathol.*, **21**, 1030 (1951)
65. Motulsky, A., *Clin. Research Proc.*, **1**, 100 (1953)
66. Harrington, W. J., Minnich, V., Hollingsworth, J. W., and Moore, C. V., *J. Lab. Clin. Med.*, **38**, 1 (1951)
67. Wilson, S. J., Eisemann, G., and Chance, J. H., *J. Lab. Clin. Med.*, **40**, 498 (1952)
68. Gugudda, G., and Pirasto, C., *Settimana. Med.*, **40**, 46 (1952)
69. Kissmeyer-Nielsen, F., *Acta Haematol.*, **9**, 337 (1953)
70. Stefanini, M., and Chatterjea, J. B., *Proc. Soc. Exp. Biol. Med.*, **79**, 623 (1952)
71. Wilson, S. J., Eisemann, G., and Chance, J. H., *Proc. Soc. Exp. Biol. Med.*, **81**, 317 (1952)
72. Stefanini, M., and Adelson, E., *Am. J. Clin. Pathol.*, **22**, 1164 (1952)

73. Stefanini, M., Chatterjea, J. B., Dameshek, W., Welch, C. S., and Swenson, O., *Blood*, **7**, 289 (1952)
74. Wright, C., Doan, C. A., Bouroncle, B. A., and Zollinger, R. M., *Blood*, **6**, 195 (1951)
75. Elliott, R. H. E., and Whipple, M. A., *J. Lab. Clin. Med.*, **26**, 489 (1940)
76. Ehrlich, L., and Schwartz, S. O., *Am. J. Med. Sci.*, **221**, 158 (1951)
77. Singer, K., and Potter, R., *J. Lab. Clin. Med.*, **34**, 1336 (1949)
78. Moolten, S. E., *N. Y. State J. Med.*, **53**, 550 (1953)
79. Robson, H. N., and Duthie, J. J. R., *Brit. Med. J.*, **II**, 971 (1950)
80. Meyers, M. C., Miller, S., Linman, J. L., and Bethell, F. H., *Ann. Internal Med.*, **37**, 352 (1952)
81. Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J., and Samuels L. T., *Arch. Internal Med.*, **88**, 310 (1951)
82. Evans, R. S., and Liu, C., *Arch. Internal Med.*, **88**, 503 (1951)
83. Stefanini, M., Perez, S. E., Chatterjea, J. B., Dameshek, W., and Salomon, L., *J. Am. Med. Assoc.*, **149**, 647 (1952)
84. Faloon, W. W., Greene, R. W., and Lozner, E. L., *Am. J. Med.*, **13**, 12 (1952)
85. Wilson, S. J., and Eisemann, G., *Am. J. Med.*, **13**, 21 (1952)
86. Davidson, L. S. P., Girwood, R. H., and Swan, H. T., *Brit. Med. J.*, **II**, 1059 (1952)
87. Havermark, N. G., and Nordenson, N. G., *Acta Haematol.*, **9**, 107 (1953)
88. Greene, R. W., Faloon, W. W., and Lozner, E. L., *Am. J. Med. Sci.*, **226**, 203 (1953)
89. Jacobson, B. M., and Sohier, W. D., *New Engl. J. Med.*, **246**, 247 (1952)
90. Jacobson, B. M., *Arch. Internal Med.*, **92**, 471 (1953)
91. Stefanini, M., and Rosenthal, M. C., *Proc. Soc. Exp. Biol. Med.*, **75**, 806 (1950)
92. Stefanini, M., and Dameshek, W., *New Engl. J. Med.*, **248**, 797 (1953)
93. Editorial, *J. Am. Med. Assoc.*, **152**, 1434 (1953)
94. Editorial, *Lancet*, **II**, 605 (1953)
95. Dillard, G. H. L., Brecher, G., and Cronkite, E. P., *Proc. Soc. Exp. Biol. Med.*, **78**, 796 (1951)
96. Minor, A. H., and Burnett, L., *Blood*, **7**, 693 (1952)
97. Braunsteiner, H., Pakesch, F., and Vetter, V., *Acta Haematol.* **8**, 304 (1952)
98. Tullis, J. L., *Blood*, **7**, 891 (1952)
99. Van Creveld, S., Paulssen, M. M. P., and Bartels, H. L. J. M., *J. Clin. Pathol.* **6**, 41 (1953)
100. Tullis, J. L., and Rochow, E. G., *Blood*, **7**, 850 (1952)
101. Tullis, J. L., *Am. J. Med. Sci.*, **226**, 191 (1953)
102. Stefanini, M., Dameshek, W., and Adelson, E., *Proc. Soc. Exp. Biol. Med.*, **80**, 230 (1952)
103. Stefanini, M., Plitman, G. I., Dameshek, W., Chatterjea, J. B., and Mednicoff, I. B., *J. Lab. Clin. Med.*, **42**, 723 (1953)
104. Hanlon, D. G., *Proc. Staff Meetings Mayo Clinic*, **27**, 273 (1952)
105. Schenken, J. R., *New Orleans Med. Surg. J.*, **154**, 477 (1952)
106. Elliott, R. H. E., and Turner, J. C., *Surg. Gynecol. Obstet.*, **92**, 539 (1951)
107. Robson, H. N., *Quart. J. Med.*, **72**, 279 (1950)
108. Dameshek, W., and Welch, S. C., *Spleen and Hypersplenism*, 2nd ed. (Grune & Stratton Publ., New York, N. Y., 84 pp., 1952)

109. Rosenthal, N., Vogel, P., Lee, S., and Lipsay, J., *J. Mt. Sinai Hosp., N. Y.*, **17**, 1008 (1951)
110. Mustard, R. L., and Chandler, G. M., *Surgery*, **34**, 101 (1953)
111. Loeb, J., Seeman, W. B., and Moore, C. V., *Blood*, **7**, 904 (1952)
112. Pearson, P. H., Peck, J. L., and Livingston, S., *Bull. Johns Hopkins Hosp.*, **91**, 341 (1952)
113. Lutwycne, V. U., and Brewerton, D. A., *Brit. Med. J.*, **I**, 1302 (1952)
114. Nizet, A., *Science*, **115**, 290 (1952)
115. Botsford, T. W., Wheeler, H. B., Newton, R. A., and Jaques, W. E., *J. Am. Med. Assoc.*, **151**, 788 (1953)
116. Chalmers, J. N. M., *Practitioner*, **168**, 235 (1952)
117. Keat, E. C. B., and Williams, T. P., *Lancet*, **II**, 79 (1951)
118. Geiger, J., *J. Am. Med. Assoc.*, **149**, 1219 (1952)
119. Nelson, M. G., *Brit. Med. J.*, **I**, 300 (1952)
120. Scalettar, H. E., and Mazursky, M. M., *N. Y. J. Med.*, **52**, 2808 (1952)
121. Karpinsky, F. E., *J. Pediat.*, **37**, 373 (1950)
122. Smadel, J. A., *Am. J. Med.*, **7**, 671 (1949)
123. Dameshek, W., *Blood*, **7**, 755 (1952)
124. Wolman, N., *Brit. Med. J.*, **II**, 426 (1952)
125. Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O., and Kahn, J., *J. Am. Med. Assoc.*, **148**, 231 (1952)
126. Claudon, D. B., and Holbrook, A. A., *J. Am. Med. Assoc.*, **149**, 912 (1952)
127. Smiley, R. K., Cartwright, G. E., and Wintrobe, M. M., *J. Am. Med. Assoc.*, **149**, 914 (1952)
128. Sturgeon, P., *J. Am. Med. Assoc.*, **149**, 918 (1952)
129. Rheingold, J. J., and Spurling, C. L., *J. Am. Med. Assoc.*, **149**, 1301 (1952)
130. Hargraves, M. M., Mills, S. D., and Heck, F. J., *Proc. Staff Meetings Mayo Clinic*, **27**, 280 (1952)
131. Loyd, E. L., *Antibiotics & Chemotherapy*, **2**, 1 (1952)
132. Cone, T. E., and Abelson, S. M., *J. Pediat.*, **61**, 340 (1952)
133. Dameshek, W., and Campbell, E. W., *Bull. New Engl. Med. Center*, **14**, 81(1952)
134. Belloni, F., *Quart. Rev. Allergy and Appl. Immunol.*, **6**, 112 (1952)
135. Lipson, L., *N. Y. J. Med.*, **52**, 586 (1952)
136. Larson, R. K., *Blood*, **8**, 16 (1953)
137. Bigelow, F. S., and Desforges, J. F., *Am. J. Med. Sci.*, **224**, 274 (1952)
138. Nussbaum, H. G., and Shulman, M. W., *Ann. Internal Med.*, **37**, 190 (1952)
139. Grandjean, L. C., *Acta Med. Scand.*, **131**, Suppl. 213, 165 (1950)
140. Kiep, C., *Deut. med. Wochschr.* (Allergy Suppl.), **77**, 9 (1952)
141. Ackroyd, J. F., *Clin. Sci.*, **10**, 1851 (1951)
142. Ackroyd, J. F., *Clin. Sci.*, **8**, 235 (1949)
143. Ackroyd, J. F., *Clin. Sci.*, **7**, 231 (1949)
144. Ackroyd, J. F., *Clin. Sci.*, **7**, 249 (1949)
145. Stefanini, M., Mednicoff, I. B., and Plitman, G. I. (To be published)
146. Grant, D. K., *Brit. Med. J.*, **II**, 128 (1953)
147. Hirsch, E. O., and Dameshek, W., *Am. J. Med.*, **9**, 828 (1950)
148. Bernhard, W. G., Gore, I., and Kilby, R. A., *Blood*, **6**, 990 (1951)
149. Stefanini, M., Plitman, G. I., and Duchenne, T. (To be published)
150. Robson, H. N., and Walker, C. H. M., *Arch. Disease Childhood*, **26**, 175 (1951)
151. Epstein, R. D., Lozner, E. L., Cobbey, T. S., Jr., and Davidson, C. S., *Am. J. Med.*, **9**, 44 (1950)

152. Singer, K., Motulsky, A., and Shanberge, J. N., *Blood*, **5**, 434 (1950)
153. Singer, K., Borstein, F. P., and Wile, S. A., *Blood*, **2**, 542 (1947)
154. Gendel, B. R., Young, J. M., and Kraus, A. P., *Am. J. Med.*, **13**, 3 (1952)
155. Meacham, G. C., Orbison, J. L., Heinle, R. W., Steele, H. J., and Schaefer, J. A., *Blood*, **6**, 706 (1951)
156. Adelson, E., and Stefanini, M. *Blood*, **7**, 700 (1952)
157. Rackow, F., Steingold, L., and Wood, J. H. F., *Acta Med. Scand.*, **143**, 137 (1952)
158. Cooper, T., Stickney, J. M., Pease, G. L., and Bennet, W. A., *Am. J. Med.*, **13**, 374 (1952)
159. Barondess, J. A., *Am. J. Med.*, **13**, 294 (1952)
160. Friedman, I. A., Kleinschmidt, W. H., and Schwartz, S. O., *Illinois Med. J.*, **101**, 212 (1952)
161. Ellman, R., and Johnson, J. H. P., *Brit. J. Tuberc.*, **46**, 214 (1952)
162. Schrijer, H., and Schillings, P. H. M., *Acta Med. Scand.*, **144**, 213 (1952)
163. Klein, F., and Lehot'an, A., *Schweiz. med. Wochschr.*, **82**, 927 (1952)
164. Kunkel, P., and Yesner, R., *Arch. Pathol.* **50**, 778 (1950)
165. Dameshek, W., *Blood*, **8**, 381 (1953)
166. Dalgleish, P. G., and Ansell, B. M., *Brit. Med. J.*, **I**, 225 (1950)
167. Balf, C. L., *Arch. Disease Childhood*, **26**, 20 (1951)
168. Lecutier, M. G., *J. Clin. Pathol.*, **5**, 336 (1952)
169. Stefanini, M., Roy, C., Zannos, L., and Dameshek, W., *J. Am. Med. Assoc.*, **144**, 1372 (1950)
170. Pitney, W. R., and Dacie, J. V., *J. Clin. Pathol.*, **6**, 9 (1953)
171. Macfarlane, R. G., and Biggs, R., *J. Clin. Pathol.*, **6**, 3 (1953)
172. Biggs, R., and Douglas, A. S., *J. Clin. Pathol.*, **6**, 23 (1953)
173. Graham, J. B., Collins, D. L., Godwin, I. D., and Brinkhous, K. M., *Proc. Soc. Exptl. Biol. Med.*, **77**, 294 (1951)
174. Soulier, J. P., and Larrieu, M. J., *J. Lab. Clin. Med.*, **41**, 849 (1953)
175. Quick, A. J., and Hussey, C. V., *Am. J. Med. Sci.*, **223**, 401 (1952)
176. Quick, A. J., Stapp, W. F., and Hussey, C. V., *J. Lab. Clin. Med.*, **39**, 142 (1952)
177. Elliott, F. R., *J. Lab. Clin. Med.*, **40**, 766 (1952)
178. Sterberger, L. A., and Maltaner, F., *Science*, **114**, 414 (1951)
179. Owren, P. A., *Scand. J. Clin. & Lab. Invest.*, **1**, 81 (1949)
180. Koller, F., Loeliger, A., and Duckert, F., *Acta Haematol.*, **6**, 1 (1951)
181. Biggs, R., and Douglas, A. S., *J. Clin. Pathol.*, **6**, 15 (1953)
182. Ware, A. G., and Stragnell, R., *Am. J. Clin. Pathol.*, **22**, 791 (1952)
183. Benthaus, J., *Klin. Wochschr.*, **29**, 517 (1951)
184. Owren, P. A., and Aas, K., *Scand. J. Clin. & Lab. Invest.*, **3**, 201 (1951)
185. Koller, F., Loeliger, A., Duckert, F., and Hu-Wang, H., *Deut. med. Wochschr.*, **77**, 528 (1952)
186. Wolf, P., *J. Clin. Pathol.*, **6**, 34 (1953)
187. Mann, F. D., *Am. J. Clin. Pathol.*, **23**, 623 (1953)
188. Bell, W., *Med. Clin. N. Amer.*, **37**, 1843 (1953)
189. Friedmann, I. S., and Schwartz, S. O., *J. Am. Med. Assoc.*, **150**, 83 (1952)
190. Stefanini, M., *Int. Record Med.*, **165**, 431 (1952)
191. Stefanini, M., *J. Mt. Sinai Hosp., N. Y.*, **19**, 619 (1953)
192. Milstone, J. H., *Medicine*, **31**, 411 (1952)
193. Laki, K., *Blood*, **8**, 845 (1953)
194. Stefanini, M., *Blood*, **6**, 84 (1951)

195. Laurell, C. B., *Blood*, **7**, 555 (1952)
196. di Nicola, P., *Blood*, **8**, 947 (1953)
197. Alexander, B., Goldstein, R., Landwehr, G., and Cook, C. D., *J. Clin. Invest.*, **30**, 596 (1951)
198. Owren, P. A., and Bjerkelund, C., *Scand. J. Clin. & Lab. Invest.*, **1**, 162 (1949)
199. Alexander, B., *Rev. d'Hématologie*, **7**, 168 (1952)
200. Owren, P. A., *Rev. d'Hématogie*, **7**, 147 (1952)
201. Duckert, F., Koller, F., and Matter, M., *Proc. Soc. Exptl. Biol. Med.*, **82**, 259 (1953)
202. Lewis, J. H., and Ferguson, J. H., *J. Clin. Invest.*, **32**, 915 (1953)
203. Stohlman, F., Harrington, W. J., and Moloney, W. C., *J. Lab. Clin. Med.*, **38**, 842 (1951)
204. Bink, A. J., and Kingsley, C. S., *Quart. J. Med.*, **21**, 19 (1952)
205. Frank, E., Bilhan, N., and Ekren, H., *Am. Internal Med.*, **33**, 467 (1950)
206. de Vries, A., Matoth, Y., and Shamir, Z., *Acta Haematol.*, **5**, 129 (1951)
207. Brennan, M. J., Monto, R. W., and Shafer, H. C., *Am. J. Clin. Pathol.*, **22**, 150 (1952)
208. Alexander, B., Goldstein, R., and Landwehr, G., *J. Clin. Invest.*, **30**, 627 (1951)
209. Alexander, B., and Goldstein, R., *Am. J. Med.*, **13**, 255 (1952)
210. Beaumont, J. L., and Bernard, J., *Presse Méd.*, **59**, 1496 (1952)
211. Frick, P. G., and Hagen, P. S., *J. Lab. Clin. Med.*, **42**, 212 (1953)
212. Campbell, E. W., and Stefanini, M., *Proc. Soc. Exptl. Biol. Med.*, **83**, 105 (1953)
213. Flynn, J. E., and Coon, R. W., *Federation Proc.*, **12**, 387 (1953)
214. Pavlovsky, A., and Simonetti, C., *Ann. Inst. Invest. Fis. Aplic. Patol. Umana*, **6**, 6 (1944)
215. Pavlovsky, A., *Blood*, **2**, 185 (1947)
216. Koller, F., Krusi, G., and Luchsinger, G., *Schweiz. Med. Wochschr.*, **80**, 1101 (1950)
217. Castex, M. R., Pavlovsky, A., and Simonetti, C., *Medicina (Buenos Aires)* **5**, 16 (1944)
218. Schulman, I., and Smith, C. H., *Blood*, **7**, 794 (1952)
219. Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., and Bates, G., *Proc. Soc. Exptl. Biol. Med.*, **79**, 692 (1952)
220. Biggs, R., Douglas, A. S., Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R., *Brit. Med. J.*, **II**, 1378 (1952)
221. White, S. G., Aggeler, P. M., and Glendening, M. B., *Blood*, **8**, 101 (1953)
222. Van Creveld, S., and Paulssen, M.M.P., *Lancet* **I**, 823 (1953)
223. Cramer, Von R., Matter, M., and Loeliger, A., *Helv. Paediat.*, *Acta*, **8**, 185 (1953)
224. Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N., *Proc. Soc. Exptl. Biol. Med.*, **82**, 171 (1953)
225. Soulier, J. P., and Larrieu, M. J., *New Engl. J. Med.*, **249**, 547, (1953)
226. Merskey, C., *Quart. J. Med.*, **20**, 299 (1951)
227. Israels, M. C. G., Lempert, H., and Gilbertson, E., *Lancet* **I**, 1375 (1951)
228. Pinniger, J. L., and Franks, R. B., *Lancet*, **II**, 82 (1951)
229. Merskey, C., and Macfarlane, R. G., *Lancet*, **I**, 487 (1951)
230. Owren, P. A., *Proc. Intern. Soc. Hematol.*, *3rd Congress*, p. 446 (Cambridge, England, August, 1951)
231. Bernfeld, P., Stefanini, M., Berkowitz, R. D., and Hennessey, F. B., *Proc. Soc. Exptl. Biol. Med.*, **83**, 311 (1953)
232. Graham, J. B., McLendon, W. W., and Brinkhous, K. M., *Am. J. Med. Sci.*, **225**, 46 (1953)

233. Stefanini, M., *Lancet*, **I**, 606 (1951)
234. Graham, J. B., and Brinkhous, K. M., *Brit. Med. J.*, **II**, 97 (1953)
235. Stefanini, M., *Blood* (In press)
236. Van Creveld, S., and Paulssen, M. M. P., *Blood*, **7**, 710 (1952)
237. McCleery, R. S. (Personal communication)
238. Dunn, D. B., and Lyons, R. N., *Med. J. Australia*, **II**, 149 (1951)
238a. Britton, R. C., and Habif, D. V., *Surgery*, **33**, 917 (1953)
239. Lawson, H. A., *New Engl. J. Med.*, **248**, 552 (1953)
240. Prentice, A. D. J., *Lancet*, **I**, 211 (1951)
241. DeSilva, C. C., and Thanabalasundaram, R. S., *Brit. Med. J.*, 86 (1951)
242. Buček, A., *Ann. Paediat.*, **177**, 111 (1951)
243. Alexander, B., Goldstein, R., Le Bolloch, A. G., Diamond, L. K., and Borges, W., *Federation Proc.*, **12**, 167 (1953)
244. Gitlin, D., Landing, B. H., and Whipple, A., *J. Exptl. Med.*, **97**, 163 (1953)
245. Gitlin, D., and Borges, W. H., *Blood*, **8**, 679 (1953)
246. Madden, R. G., and Gould, R. G., *Federation Proc.*, **12**, 252 (1952)
247. Favre-Gilly, J., Bret, J., and Borel-Mihlet, J., *Sang*, **22**, 278 (1951)
248. Hartmann, R. C., *Bull. Johns Hopkins Hosp.*, **91**, 49 (1952)
249. Stefanini, M., Chatterjea, J. B., and Dameshek, W., *Proc. Intern. Soc. Hematol.*, *4th Congress* (Buenos Aires, Argentina, September, 1952)
250. Seegers, S. H., *Arch. Biochem. and Biophys.*, **36**, 448 (1952)
251. Tocantins, L. M., Carroll, R. T., and Holburn, R. H., *Blood*, **6**, 720 (1951)
252. Stefanini, M., Chatterjea, J. B., and Salomon, L., *Proc. Soc. Exptl. Biol. Med.*, **78**, 274 (1951)
253. Stefanini, M., and Salomon, L. (To be published)
254. Bell, W. N., *Blood*, **6**, 1199 (1951)
255. Stefanini, M., Campbell, E. W., Plitman, G. I., and Salomon, L., *Bull. New Engl. Med. Center*, **15**, 23 (1953)
256. Waldenström, J., *Acta Med. Scand.*, Suppl. **266**, 931 (1952)
257. Schaub, F., *Schweiz. med. Wochschr.*, **82**, 890 (1952)
258. Conley, C. L., and Hartmann, R. C., *J. Clin. Invest.*, **31**, 621 (1952)
259. Collins, I. S., and Ferriman, D. G., *Lancet*, **II**, 712 (1952)
260. Mueller, J. R., Ratnoff, O., and Heinle, R. W., *J. Lab. Clin. Med.*, **38**, 254 (1951)
261. Singer, K., Mond, E., Hyman, J., and Levy, R. C., *Blood*, **5**, 1135 (1950)
262. Frommeyer, W. B., Epstein, R. D., and Taylor, F. H. L., *Blood*, **5**, 401 (1950)
263. Kupfer, H. G., Thagard, R., Irvin, H., Lipford, D., and Parker, J. B., *Virginia Med. Monthly*, **79**, 629 (1952)
264. Van Creveld, S., Horweeg, P. G., and Paulssen, M. M. P., *Blood*, **8**, 125 (1953)
265. Frick, P. G., *Blood*, **8**, 598 (1953)
266. Pons, R., Jr., and de Torregrosa, M. V., *Blood*, **7**, 20 (1952)
267. Reimann, F., *Acta Med. Scand.*, **107**, 95 (1941)
268. Stefanini, M., *Blood*, **7**, 1044 (1952)
269. Favre-Gilly, J., Potton, F., and Potton-Lafuma, M. M., *La Fibrinolyse et les Diathèses Hémorragiques Fibrinolytiques* (Camogli. Publ., Lyons, France, 1952)
270. Mullertz, S., and Lassen, M., *Proc. Soc. Exptl. Biol. Med.*, **82**, 264 (1953)
271. Soulier, J. P., Mathey, J., Le Bolloch, A. G., Daumet, P., and Fayet, H., *Rev. d'Hemat.*, **7**, 30 (1952)
272. Coon, W. W., and Hogdson, P. G., *Surg. Gynecol. Abstet.*, **97**, 717 (1952)
273. Friesen, S. R., Harsha, W. N., and McCroskey, C. H., *Surgery*, **32**, 620 (1952)
274. Ratnoff, O. D., *J. Clin. Invest.*, **31**, 521 (1952)

275. Tagnon, H. J., Whitmore, W. F., Jr. and Schulman, N. R., *Cancer*, **5,** 9 (1952)
276. Tagnon, H. J., Whitmore, W. F., Jr., Schulman, P., and Kravitz, S. P., *Cancer*, **6,** 63 (1953)
277. Stefanini, M., and Gendel, B. R., *Clin. Research Proc.*, **1,** 5 (1953)
278. Peckham, C. H., and Middlebrook, L. F., *Am. J. Obstet. Gynecol.*, **65,** 644 (1953)
279. Ratnoff, O. D., Lauster, C. F., Sholl, J. G., and Schilling, M. O., *Am. J. Med.*, **13,** 111 (1952)
280. Weiner, A. E., Reid, D. E., Roby, C. C, and Diamond, L. K., *Am. J. Obstet. Gynecol.*, **60,** 1015 (1950)
281. Vecchietti, G., *Riv. ostet. e ginecol.*, **8,** 443 (1953)
282. Ratnoff, O. D., and Vosburgh, G. J., *New Engl. J. Med.*, **247,** 970 (1952)
283. Schneider, C. L., *Am. J. Obstet. Gynecol.*, **65,** 245 (1953)
284. Schneider, C. L., *Surg. Gynecol. Obstet.*, **92,** 27 (1951)
285. Reid, D. E., Weiner, A. E., and Roby, C.C., *Am. J. Obstet. Gynecol.*, **66,** 468 (1953)
286. Weiner, A. E., Reid, D. E., and Roby, C. C., *Am. J. Obstet. Gynecol.*, **66,** 475 (1953)
287. Lepage, F., Eyquem, A., and Petit, P. F., *Rev. d'Hémat.*, **7,** 72 (1952)
288. Kaeser, O., *Rev. d'Hémat.*, **7,** 55 (1952)
289. Conley, C. L., Ratnoff, O. D., and Hartmann, R. C., *Bull. Johns Hopkins Hosp.*, **88,** 402 (1950)
290. Stefanini, M., and Salomon, L. (To be published)

ENDOCRINOLOGY[1,2,3]

By Louis J. Soffer and J. Lester Gabrilove

*Department of Endocrinology of the Medical Service, The Mount Sinai Hospital,
New York, New York*

The Adenohypophysis

Cytology and histochemistry.—Purves & Griesbach (1) applied the Mc-Manus periodic acid-Schiff (PAS) reagent method for staining glycoproteins to the study of adenohypophyseal cytology in the rat. With the usual staining techniques the basophile cells are stained blue because of the large amounts of ribonucleic acid. In addition, these cells contain glycoproteins which stain with the PAS as well as with the analine blue dye of the Mallory technique (azan). On the basis of these studies two types of glycoprotein containing cells were distinguished. The "gonadotroph" is oval or round and is located essentially on the lower surface of the gland and in the upper part in relation to the pars intermedia. These cells presumably secrete gonadotropin, probably follicle stimulating hormone (FSH), and possibly luteinizing hormone (LH). This observation is supported by the fact that these cells are the source of the castration cells of gonadal deficiency and are inhibited in functional activity following the administration of estrogen. Purves & Griesbach further correlated the PAS reaction of these cells with assays of the gland for gonadotropin under varied experimental conditions. The second type of cell, the "thyrotroph," is polyhedral in shape and is located centrally. The intensity of the PAS staining reaction was similarly found to vary with the content of thyrotropin under circumstances of thyroid excess and deprivation. The glycoprotein staining content of these cells was decreased by thyroid administration and the cells were altered into the so-called thyroidectomy cells following removal of the thyroid. Purves & Griesbach suggest that no other hormone except for these specific glycoproteins are elaborated by these cells.

In further studies these observers noted that the Gomori stain specifically stains and differentiates thyrotropic hormone from gonadotropin (2, 3). They could find no evidence, as suggested by Halmi, that the cells staining with the Gomori reagent secrete adrenocorticotropin (ACTH) (4). In a subsequent communication Halmi (5) concurred in the thesis of Purves & Griesbach that his so-called "beta" cells were "thyrotrophs" and the "delta" cells "gonadotrophs." Purves & Griesbach, he observed, had correctly pointed out the loss of thyrotropin in the thyrotroph cells in long

---

[1] The survey of literature pertaining to this review was completed in June, 1953.

[2] The following abbreviations are used in this chapter: FSH for follicle stimulating hormone; LH for luteinizing hormone; ACTH for adrenocorticotropin; TSH for thyroid stimulating hormone.

[3] The gonads are not considered in this review.

standing hypothyroidism. Such cells do not stain with the Gomori stain and only to a slight extent with the McManus glycoprotein stains. This observation is of interest in that following gonadectomy the gonadotrophs are high in glycoprotein, in contrast to the low concentration of thyrotropin in the thyrotroph cells following thyroidectomy (1).

These findings bring up for review the relation of the basophil cells and Crooke's changes to adrenocortical function. In patients treated with ACTH[2] and cortisone increased basophile counts and Crooke's changes similar to those found in Cushing's syndrome have been observed (6, 7, 8). In the light of Purves & Griesbach's work, Golden & Bondy (8) reexamined this question. These authors found that the administration of cortisone or cold stress, but not ACTH, in the rat increased the percentage of pituitary basophiles. However, all three agents induced the Crooke's changes. It is thus apparent that basophilia and the Crooke's changes are dissociated and neither necessarily reflects demands for endogenous ACTH production. In addition, the hyaline masses stain histochemically for glycoprotein and are, therefore, not ACTH, since this hormone is not a glycoprotein.

In summary, then, the available evidence as of this moment would suggest that in the rat the basophilic cells are concerned with the elaboration of thyrotropin, FSH,[2] and perhaps LH.[2] The relationship of these cells to the secretion of ACTH must be held in abeyance until more precise techniques become available for the identification of this latter fraction.

Growth hormone.— In a recent review Li (10) summarized the chemical and biological properties of growth factor. Unlike the glycoproteins TSH,[2] FSH, and LH, this hormone is a simple protein with a molecular weight (ox growth hormone) of 44,000 and an isoelectric point of 6.5. This fraction contains 15.65 per cent nitrogen and 1.3 per cent sulfur. The hormonal activity is destroyed by pepsin and trypsin. It is unstable in boiling water and is more stable in alkali than in acid media. Iodination of the hormone abolishes the growth promoting ability, indicating the importance of the tyrosine groups in its biological activity. The physical and biological properties of the Wilhelmi, Fishman & Russell (11) crystalline preparation are identical with those of the pure amorphous Li fraction (10). Li has summarized the biological functions of growth hormone:

"(a) Promotion of continuous body growth in hypophysectomized and normal rats; (b) Retention of nitrogen in either normal, hypophysectomized, fractured, or diabetic rats; (c) Decrease in urinary phosphorus excretion in rats; (d) Elevation of inorganic phosphorus and alkaline phosphatase concentrations in the plasma; (e) Decrease in free amino acid content in the plasma; (f) Increase of fasting ketone bodies in the urine and blood; (g) Increase of water and protein content of whole animal with a decrease in fat indicating a true growth; (h) Thymus hypertrophy in normal and hypophysectomized rats. Liver hypertrophy in normal rats but not in hypophysectomized animals; (i) Increase in the ribonucleic acid in the liver and the turnover rate of nucleic acid in the thymus; (j) Enhancement of chon-

drogenic and estrogenic processes in the epiphyseal cartilage of the tibia. Direct influence on bone growth; (k) Increased uptake and turnover of phosphorus and calcium in bone; (l) Production of glycosuria and hyperglycemia in cats and dogs; (m) Production of permanent diabetes in dogs; (n) Maintenance of fasting muscle glycogen in adult hypophysectomized rats; (o) Contra-insulin effect in rats and anti-insulin action in hypophysectomized dogs; (p) Production of hypoglycemia in fasting normal rats; (q) Inhibiting glycogenesis in rat diaphragm muscles in the presence of insulin; (r) Increase in liver phospholipid turnover; (s) Increase in liver fat during fasting; (t) Production of tumor in normal but not in hypophysectomized rats after chronic treatment."

Li has employed the effect of growth hormone on the proximal epiphyseal tibial cartilage of the hypophysectomized rat as an assay method. With this technique the plasma of adult human subjects was reported to contain 0.1 µg. of growth hormone per ml. This author further found that thyroxin acted synergistically with growth hormone in promoting bone growth in hypophysectomized rats, the combined measures resulting in more growth than the sum of both factors employed individually (10, 12). It should be noted, however, that thyroxin alone exercises a significant effect on the tibia test (12).

More recent studies by Li and his group and by other investigators have further augmented the aforementioned observations. Sonenberg et al. (13) labelled growth hormone with I^{131} without loss of biologic activity. Following intracardiac administration to normal rats, significant concentrations of the radioactive hormone were found in the pancreas, adrenal, thyroid, kidney, liver, and spleen.

Growth hormone was found to induce retention of sodium chloride and potassium in normal female (15, 57) and in diabetic male and bilaterally adrenalectomized rats (16, 57). This might be expected, since growth requires nitrogen and potassium for intracellular components and sodium for the extracellular space. In the hypophysectomized rat, growth hormone results in an increase in the thiocyanate space without any change in the serum sodium level nor increase of the muscle sodium content (17).

Russell (18) attempted to define the site of action of growth hormone on protein metabolism. She measured the effect of growth hormone on the rate of urea formation in nephrectomized rats under basal conditions and following the intravenous administration of casein hydrolysate. Under the first set of circumstances no effect was noted on urea formation. However, growth hormone decreased the rate of urea formation following the administration of casein hydrolysate. This author, therefore, concluded that growth hormone exerts an effect on the tissue retention of amino acids rather than on their catabolism.

The studies of Bartlett and coworkers suggest that the growth hormone regulates the intracellular synthesis of protein by promoting amino acid storage (25, 65). This conclusion is supported by the increased nitrogen pool,

the decrease in amino acid catabolism, and increased rate of protein synthesis observed after growth hormone administration (66). In the thyroidectomized rat, growth hormone has little effect on muscle formation but does increase the protein content of the skin (20). This hormone may increase the muscle weight of the intact rat, but muscle performance is reduced (68).

The effect of growth hormone on the metabolism of calcium was investigated in the hypophysectomized rat (19). Ca^{45} was administered intravenously and the animals killed 2 and 24 hr. later. In the 2 hr. group, although the serum levels of Ca^{45} were identical in the control and growth hormone-treated animals, the tibias of the latter took up twice as much Ca^{45} as did the controls. However, the total calcium ash was the same in both groups. By radioautography an intense line of Ca^{45} could be demonstrated in the proximal tibial epiphyseal plate. No difference in effect was observed on the urinary or fecal excretion of the radioactive ion. In the animals sacrificed after 24 hr. the administration of growth hormone resulted in a decrease in the serum level of Ca^{45} in young hypophysectomized animals. However, no such changes were observed in the intact rats. Growth hormone exercised no effect on the uptake of Ca^{45} by the tibias of intact rats, but did increase the uptake to normal levels in hypophysectomized rats (116).

Selye has demonstrated that the administration of growth factor to rats will counteract the body weight loss and involution of the thymus, spleen, and liver induced by subtotal x-ray dosage (22) as well as the inhibition of growth caused by multiple sterile turpentine abscesses (21). This worker has also reported that growth hormone exerts a protective effect on the spread of tuberculosis in both the normal and the cortisone-treated rat (56). Ershoff was unable to promote weight gain with growth hormone in immature rats exposed to cold (63). Smith *et al.* were able to increase body and tumor weight with growth hormone in mice bearing transplantable adenocarcinoma (64).

Following hypophysectomy in the rat there develops an anemia associated with hypoplasia of the erythrogenic elements (23), an increase of the lymphocytic elements, and a decrease of the neutrophile myelocytes of the marrow (23, 120). Growth hormone fails to prevent or correct this anemia (24), although cobalt is reported to do so (104).

The growth hormone generally available for experimental purposes exercises a diabetogenic effect (26, 27). However, it has become apparent that marked species variations exist. In the dog and cat temporary and even permanent diabetes can be induced with this fraction (26, 37, 38). Young (26, 33) has emphasized the ease with which diabetes can be produced with growth hormone in the adult animal, whereas enhanced growth rather than diabetes occurs in the immature animal. This author has suggested that diabetes follows the administration of growth hormone when the full growth response cannot be achieved. It is interesting to note that pregnant and lactating animals fail to develop diabetes following administration of growth hormone (26). Such therapy usually results in growth of both the pregnant mother and the fetus (51, 58, 59).

Overdosage with ACTH or certain adrenal cortical steroids prevents a full growth response to growth hormone (27). As pointed out by Engel (27), the diabetogenic effect of pituitary extracts is not observed in the adrenalectomized cat but is restored following administration of whole adrenal cortical extract (31, 27). In the rat diabetes may be induced by anterior pituitary extract or growth hormone following partial depancreatectomy (29). As in the cat, adrenalectomy in such animals prevents the diabetogenic effect of anterior pituitary extract, but diabetogenicity is restored if adrenal cortical extract is administered (32). In the rat, the lack of a diabetogenic effect of growth hormone is in sharp contrast to the relative ease with which glycosuria follows the administration of ACTH or corticosteroids. However, if the rat is force fed and given ACTH in amounts insufficient to produce glycosuria the addition of growth hormone will induce hyperglycemia and glycosuria (27). It has been suggested that the different response of the dog and cat as contrasted to that of the rat lies also in the ability of the islet cells of the latter to undergo hyperplasia readily in response to hyperglycemia. The pancreas of the former animals, particularly the cat, is probably unable to sustain an adequate level of insulin secretion to counteract the effect of diabetogenic agents (27, 30). It is still not known whether the growth-promoting action of growth hormone may be mediated through its effect in causing increased insulin secretion, and when the pancreas is no longer capable of responding adequately diabetes develops (26).

De Bodo & Sinkoff (151) have been particularly interested in the effect of growth hormone in the hypophysectomized dog. They found that growth hormone abolished the insulin hypersensitivity of such animals and produced an insulin resistant diabetes (28, 34, 35). In contrast, cortisone, administered in amounts sufficient to restore the carbohydrate metabolism of adrenalectomized dogs to normal, abolished the insulin hypersensitivity and the secondary hypoglycemia induced by a glucose tolerance test in hypophysectomized dogs (41, 42) without inducing either insulin resistance or diabetes (36). Concomitant administration of a diabetogenic growth hormone preparation and cortisone failed to alter the effects noted with cortisone alone. Insulin resistance and diabetes were not observed during the combined treatment, suggesting to these investigators that a balance exists between growth hormone and the adrenocortical steroids in the regulation of carbohydrate metabolism in the normal organism (36). It should be pointed out, however, that growth hormone may produce an initial hypoglycemia in the normal rat (40) and in the acutely depancreatized dog (39). It is possible that this results from the removal of nitrogen from the metabolic pool under the influence of growth hormone. Nitrogen is thus not available for gluconeogenesis. It has also been suggested that under the influence of a marked increase in the secretion of insulin in the depancreatized dog, circulating insulin may still have been present during the initial experimental period. In regard to the interrelation of growth hormone and insulin the experiments of Milman and co-workers (67) are pertinent. These investi-

gators found that in depancreatized cats on a constant food and insulin intake nitrogen storage varied with the amount of growth hormone administered. In the absence of insulin, however, growth hormone has no nitrogen-retaining effect. Insulin is apparently, therefore, necessary for the nitrogen-retaining effect of growth hormone.

Hypophysectomized dogs showing adrenal cortical atrophy (267) manifest hypersensitivity to insulin, a secondary hypoglycemia in the glucose tolerance test, and a diminished response to the hyperglycemic effect of epinephrine (Adrenalin). ACTH and cortisone abolish these changes. However, in some dogs there ensues some degree of insulin resistance, a diabetic glucose tolerance curve, and an increased response to epinephrine. It is likely, therefore, that the adrenal cortical atrophy in the hypophysectomized dog plays a significant role in the production of insulin hypersensitivity (41). Since the adrenalectomized dog is more sensitive to insulin than is the intact animal but less so than the hypophysectomized one, there may be an anterior pituitary factor other than ACTH that is of importance in the production of this metabolic abnormality (42).

It is of some parenthetical interest that growth hormone exerts a diabetogenic and growth-promoting action when administered to the chick embryo (51). This is of interest in view of the suggestion that fetal gigantism observed in human diabetic or potentially diabetic mothers is due to excessive maternal growth-hormone production (52, 59).

Growth hormone (10, 62) (a) depresses the RQ of fasting hypophysectomized and fed normal rats; (b) prevents severe loss of muscle glycogen observed in fasting hypophysectomized animals; (c) depresses glucose uptake of isolated diaphragms of normal and hypophysectomized rats; (d) exerts no effect on the *in vitro* uptake of glucose by the rat diaphragm but inhibits the action of insulin; (e) exerts its greatest effect on cardiac glycogen, while insulin influences diaphragm glycogen chiefly (69). These authors doubt that growth hormone exerts its effect as a result of decreased carbohydrate oxidation and that these effects are mediated or dependent on insulin.

In only relatively few instances has growth hormone been employed in the human subject. Carballeira *et al.* (43) studied the effect of a single intravenous injection of growth hormone in fasting patients given an intravenous infusion of amino acids. They noted a rapid, sustained lowering of the blood amino acid nitrogen levels and of urinary amino acid nitrogen excretion, a transient hyperglycemia, and an increase in the ketone bodies in the blood. No effect was noted on the blood phosphorus, serum aklaline phosphatase, or blood eosinophiles. Bennett and co-workers, employing growth hormone, failed to induce nitrogen retention or alteration in the blood glucose level in an hypophyseal dwarf (44). No effect on nitrogen balance was observed by Lewis and his group in a cretin and a dwarf (45). In a patient with pseudo-panhypopituitarism Crispell & Parson (418) reported minimal changes in carbohydrate metabolism. Shorr *et al.* (46), however, recently reported significant storage of nitrogen, calcium, and phosphorus, impairment of glucose

tolerance, and development in insulin resistance in two girls given crystalline growth hormone prepared by the Wilhelmi method. In one subject glycosuria occurred. Administration of a Raben-Westermeyer preparation of growth hormone was without effect on nitrogen or carbohydrate metabolism in one of the girls responding to the Wilhelmi preparation.

Raben & Westermeyer have prepared a growth hormone said to be free of diabetogenic factor (47, 48). This fraction is virtually free of ACTH, TSH, gonadotropin, and posterior lobe principles, and contains only traces of luteotropin, adipokinin, and intermedin. Glycosuria could not be induced in dogs with this preparation, although it was equal in growth-promoting activity to the Li and Wilhelmi preparations. With this growth fraction, these investigators induced nitrogen and phosphorus retention in a 26-year-old woman with hypopituitarism. No effects on carbohydrate metabolism were observed (49).

The claim of Raben & Westermeyer as to the dissociation of growth promoting activity and diabetogenicity is disputed by Reid (53, 54, 60). Employing various purification procedures based on the Li and Wilhelmi methods this author found that the ratio of diabetogenic activity in the cat to growth-promoting activity in the rat remained constant. With various inactivating procedures the two functions were lost to the same degree. He suggested that the biological activity of the growth hormone molecule is dependent on the activity of the ϵ-amino groups (lysine) but not on that of the α-amino groups (alanine and phenylalanine). The COOH terminal groups are probably not essential for the biologic activity of growth hormone (55).

Kinsell *et al.* (50), employing growth hormone prepared by Raben & Westermeyer, were unable to observe any significant effects.

In a human subject with hypoglycemia resulting from a pancreatic islet cell tumor, the use of growth hormone permitted a reduction in carbohydrate intake necessary to prevent attacks, although growth hormone did not relieve the attacks. No hyperglycemic effect of growth hormone was observed (61).

The totally hypophysectomized dog has an impaired ability to handle water loading, which is improved by growth hormone (70). This, however, is not observed in rats (71). The Raben-Westermeyer growth hormone was without effect on nitrogen retention and on water exchange in a patient with diabetes insipidus who subsequently developed adenohypophyseal insufficiency (72).

Acromegaly.—Rheumatism and joint pains in acromegaly were originally described by Marie and other early workers. Kellgren, Ball & Tutton (73) have recently reviewed 25 instances of the disease and have studied them clinically and pathologically with emphasis on the articular and limb changes. Of the 25 patients, only nine had never had any joint manifestations. In all patients some enlargement of the limb joints was noted. The muscles, although well developed, were poor in power and strength. There appeared to be two types of acromegalic arthopathy. In one there are bony

outgrowths and deformity of the bone ends leading to limitation of motion. This is uncommon and occurs in long-standing disease. The other form is characterized by pain in the back and limbs, soft tissue enlargement of the joints with excessive and abnormal mobility, synovial thickening and recurrent effusions. On x-ray examination, the characteristic finding is an increased joint space with remodelling of the bone ends. The sedimentation rate is frequently rapid, and it is of interest to note that an increase in the sedimentation rate can be induced experimentally with growth hormone. Peripheral nerve lesions occur commonly. In three patients a bilateral median nerve lesion was found, and paresthesias were observed in six others. The peripheral arteries and veins were thickened and tortuous in 13 patients. Hypertension was a common finding. Fourteen patients presented a history of Raynaud-like attacks. On pathologic examination the periarticular soft tissues show a noninflammatory fibrous hyperplasia. The joints reveal a striking overgrowth of the articular cartilage and soft tissues together with remodelling of the bones. Hyperplasia and softening of the cartilage may lead to the formation of ulcers with undermined edges. The theoretical relationship of growth hormone to tumor formation is lent some clinical support by a report of the association of a malignant eosinophilic adenoma of the adenohypophysis occurring in the presence of a primary carcinoma of the liver (75). Even more interesting, however, is the group of cases of pituitary tumors, chiefly eosinophilic adenomas, found in association with other endocrine tumors, particularly those of the parathyroid and pancreatic islands (76). At least 14 well-documented cases were collected from the literature. Of these, six were instances of pituitary and parathyroid tumor, five of the cases presenting the classical manifestations of acromegaly. Two were instances of acromegaly and pancreatic islet cell tumor. In one instance a parathyroid tumor and islet cell adenoma was found. There were five instances of all three tumors, four of these being typical acromegalics. Of the eight cases reported from the Mayo Clinic (76) only one had acromegaly. In this group four had demonstrable pituitary tumors, while parathyroid tumors were present in all eight patients and five had islet cell tumors. Of this last group of five patients, three had definite hypoglycemic episodes. An instance of acromegaly in association with a pheochromocytoma (77) is of interest, particularly in view of the experimental production of adrenal medullary tumors by growth hormone (10).

McCullagh and co-workers have reported an interesting observation in a patient with acromegaly and diabetes mellitus. The diabetes disappeared as the acromegaly improved following treatment with estrogen (79). However, since the natural course of acromegaly may include necrosis of the tumor with the subsequent development of hypopituitarism, this unusual response to estrogen must be regarded with some caution. We have had one similar instance in a patient treated with radiotherapy who showed a similar response but later developed full-blown hypopituitarism. A case illustrating such a sequela has also been recently reported by Thompson et al. (80).

An interesting report that waits confirmation is that of Villaverde that the clinical manifestations of acromegaly improved following injections of an extract of *Necator americanus* (78).

In view of occasional association of acromegaly with galactorrhea and amenorrhea, it is important to differentiate this clinical picture from the syndrome of amenorrhea with estrogenic insufficiency, galactorrhea, and a decreased urinary excretion of gonadotropins (81, 82). Such a syndrome, first reported in 1932 (83), has recently been emphasized by Forbes and her co-workers (81) and by Argonz & del Castillo (82). The genesis of this syndrome is unknown. It has been suggested that it represents hyperfunction of the eosinophilic cells of the adenohypophysis. A syndrome closely allied to the one under discussion occurs *post partum* and is thus identified (Chiari-Frommel). The syndrome may also be noted in association with hypophyseal or juxta sella tumor and in Simmonds' disease.

Hypopituitarism.—Sheehan & Summers (84) recently have reviewed the syndrome of hypopituitarism based on pathologically proved cases of complete destruction of the adenohypophysis. They group the lesions into five categories: (*a*) acute, (*b*) subacute, (*c*) chronic fibroid, (*d*) surgical hypophysectomy, and (*e*) cysts and tumors. The acute lesions are almost always due to necrosis of the adenohypophysis, usually following *post partum* hemorrhage. The subacute lesions include gumma, tuberculoma, granulomas of unknown etiology, and various miscellaneous lesions including abscesses, sarcoidosis, leukemic infiltration, etc. The chronic fibroid lesions may include various healed stages of the acute and subacute variety, particularly *post partum* necrosis, various fibrotic scars of unknown etiology, healed fractures of the base of the skull. The cysts and tumors, which may be intra- or extra-sellar, include simple and cholesterol cysts, craniopharyngiomas, and pituitary adenomas. Of these only those instances, 95 in number, proven pathologically, were included in order to define the syndrome of true hypopituitarism. The life expectancy in this group was as given in Table I.

TABLE I

Life Expectancy of Pathologically Proven Cases of Complete
Destruction of the Adenohypophysis

Life Expectancy (Years)	1 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 40	
Number of Patients	12	18	18	10	8	8	6	Total 80

On pathological examination, the adrenals, thyroid, gonads, and genital tract were found to be atrophic. In additon, there was striking atrophy of most of the viscera.

TABLE II

Weights of Endocrine Glands in Hypopituitarism

	Hypopituitarism Weight in Grams	Normal Weight in Grams
Adrenals	4.7	10 to 15
Thyroid	7	20 to 30
Ovaries	3.8 to 5.4	10 to 15

The patients were generally well nourished and cachexia was uncommon and usually due to the effects of a prolonged debilitating lesion rather than to hypopituitarism. Other clinical features included complete and permanent loss of sex function, decrease in size of the gonads and genital tract, amenorrhea, impotence, and loss of libido, and complete loss of pubic and axillary hair. There was an absence of normal skin pigment and a lack of response to solar radiation. The facies were flabby, with thinning of the eyebrows and pallor of the cheeks. Sweating was reduced or absent, and there was a loss of greasiness of the axilla, increased cold sensitivity, physical weakness and torpidity, together with a soft, slow speech. The basal metabolic rate was generally markedly reduced. The urinary excretion of the neutral 17-keto-steroids was less than 1 mg. per day. The insulin tolerance test was characterized by insulin sensitivity and hypoglycemic unresponsiveness, and, frequently, a tendency to spontaneous hypoglycemia and coma. Water diuresis was inadequate, and patients often manifested a macrocytic or normocytic hypochromic anemia. The blood cholesterol was moderately elevated and serum sodium and chloride levels often reduced. Hypopituitarism is often confused with pseudohypopituitarism, selective failure of the adenohypophysis, nephritis, other causes of hypoglycemia and coma, mental illness, Addison's disease, and primary myxedema. Sheehan & Summers emphasize that cachexia only infrequently occurs in hypopituitarism, thus permitting differentiation from anorexia nervosa (87, 88, 100).

Perkins & Rynearson (85) have reviewed the "practical aspects of insufficiency of the anterior pituitary gland in the adult." They quote extensively from Sheehan & Summers (84) and also review the previous literature. The clinical description follows that of Sheehan & Summers. The laboratory procedures useful in the differential diagnosis are discussed in detail. These authors emphasize that hypoglycemia, an increased sugar tolerance, and hypoglycemic unresponsiveness are common. They caution that the use of the insulin tolerance test is fraught with danger and must be carried out with great care. Generally, the diagnosis of hypopituitarism is best established by demonstrating simultaneous existence of tropic end organ insufficiency (86). The basal metabolic rate is reduced, the serum protein-bound iodine level is lowered, and the uptake of I_{131} by the thyroid is reduced. Following the administration of thyroid stimulating hormone (TSH) there is an increase

in the thyroidal collection of I_{131}. This procedure is particularly important for the differentiation of primary from secondary hypothyroidism (91). Adrenal function is measured by the water tolerance test, the ACTH eosinophile test, the urinary excretion of the neutral 17-ketosteroids and of the 11-oxygenated steroids. Gonadal function may best be studied by vaginal smear, endometrial biopsy, sperm count, testicular biopsy, and the urinary excretion of gonadotropins.

Certain important considerations must be borne in mind: (a) Tropic failure of all three end organs may exist without hypopituitarism (pseudohypopituitarism); (b) The picture of hypopituitarism may resemble primary failure of the end organs. This can be distinguished from hypopituitarism by the administration of the purified pituitary fraction, noting its effect on the responsiveness of the target gland. A functional response would indicate adequacy of the target gland and failure of the pituitary secretion of that fraction. The differentiation of primary from secondary myxedema is discussed by Soffer & Gabrilove (89). In primary myxedema the urinary excretion of gonadotropins may be reduced and adrenal cortical function tests impaired. When such is the case the differential diagnosis is best established by the administration of TSH. The thyroid stimulating hormone will increase the thyroidal uptake of I_{131} in pituitary insufficiency but will not affect this function in primary myxedema. The prolonged use of TSH or of thyroid extract may produce adrenal crisis in patients with hypopituitarism (304).

Perkins & Rynearson (85) emphasize that at present treatment consists essentially of specific end organ replacement therapy. They recommend the use of cortisone or, less preferably, desoxycorticosterone acetate, and thyroid extract in gradually increasing dosages. Testosterone is administered to patients for its anabolic effect, although they suspect that it may at times cause reactivation of a chromophobe adenoma. In women estrogens have been employed to initiate cyclic bleeding. Other reports of a similar nature on hypopituitarism include that of Paschkis & Cantarow (90).

A very stimulating article dealing with causes of hypopituitarism has been published by Hubble (92). He divides hypopituitarism into genetic, nutritional, and psychogenic groups, and that resulting from actual destruction of the adenohypophysis. Genetic hypopituitarism includes those instances in which a deficiency or absence of one of the pituitary hormones occurs as a developmental defect. Instances of this group include hypogonadotropic hypogonadism (93), hypothyrotropic hypothyroidism (94, 113), and dwarfism (92, 96). As yet no instance of selective adrenocorticotropic insufficiency has been reported. Nutritional and psychogenic hypopituitarism include anorexia nervosa, malnutrition, and abnormal psychogenic states with the production of signs and symptoms of hypopituitarism. There is clinical evidence to suggest that the elaboration of gonadotropins may be suppressed in malnutrition and in abnormal psychic states. There is some evidence that under these circumstances the elaboration of growth hormone may also be diminished. Evidence is lacking, however, that these states can

produce an actual deficiency in the secretion of thyrotropic or adrenocortico-tropic hormones, although it must be granted that in anorexia nervosa a low basal metabolic rate and some decrease in the daily urinary excretion of the neutral 17-ketosteroids occurs. In destructive lesions of the adenohypophysis, gonadal failure frequently, although not invariably, occurs first, and thyroidal and adrenocortical insufficiency may be minimal and slowly developing. It is particularly interesting in this regard to note the report of Oelbaum (97), who in six instances of Sheehan's syndrome observed one case with selective mild adrenocortical failure, one with marked gonadal failure, one instance with moderate adrenocortical and thyroidal failure but no evidence of gonadal failure, while the remaining three patients showed varying degrees of failure of all tropic end organs. This has similarly been our experience and the experience of others (87, 88, 90). It is perhaps germane to note that not all instances in which more than one tropic end organ is found to be insufficient are necessarily instances of hypopituitarism. In the presence of primary hypothyroidism, secondary gonadal and adrenal cortical failure is not uncommon (114, 115). In such patients improvement in the myxedematous state will result in prompt improvement in gonadal and adrenal cortical function.

Hubble (92) also discusses the dissociation of adenohypophyseal hormonal failure, pointing out that gonadal failure occurs when 80 per cent of the secreting pituitary cells are destroyed. Under these circumstances the secretion of ACTH and TSH may continue. This author points out, however, that the thyroid and the adrenal cortex are capable of some degree of autonomous function, which may perhaps explain the persistence of function in these glands. He believes that those instances of Sheehan's syndrome in which sexual hair decreases and the urinary excretion of the neutral 17-ketosteroids falls coincidentally with the reduction in sexual function support Albright's thesis of the role of LH on the elaboration of androgens by the adrenals. Albright & Elrich (98) have suggested that all anterior pituitary hormonal fractions with the exception of FSH and LH arise from the eosinophile cells. Hubble reports a case of hemachromatosis with hypogonadism in which iron was deposited only in the basophile cells of the adenohypophysis. In this patient adrenal and thyroid functions were intact. The urinary excretion of gonadotropins, however, was below 6 m. u. u. per 24 hr. There was considerable testicular atrophy. The urinary excretion of the neutral 17-ketosteroids was 1.4 mg. in 24 hr. Microscopic examination of the pituitary revealed the presence of iron pigment in the basophile cells, while none was found in the chromophobes or eosinophiles. In the adrenal, the zona glomerulosa contained some iron pigment, the zona fasciculata was quite normal, while the reticular zone had almost entirely disappeared. The thyroid gland was normal, but the testis showed absence of Leydig cells and tubular degeneration. This case is advanced by Hubble as supporting the view that FSH and LH are the only hormones formed by the human pituitary basophile cell, and that LH stimulates the secretion of androgens by the adrenals.

The studies of Sheehan on post partum necrosis and hypopituitarism have stimulated other workers to investigate the role of shock and hemorrhage on pituitary function in clinical states other than pregnancy (101). Plaut (99) observed some areas of pituitary necrosis in 12 of 149 autopsies of male patients. These areas varied from less than 1 mm. to 5 mm. in diameter. There was no evidence of thrombosis or embolism, and no correlation with clinical disease was evident. He believes the necrosis seen in Sheehan's syndrome is an exaggeration of the process that often takes place in the last days of life in nonpregnant women and in men.

That regeneration can occur in the pituitary is demonstrable by clinical experience. An instance of the therapeutic value of subsequent pregnancy on adenohypophyseal function is reported by Murdoch & Govan (102). It is obvious that the original lesion must not be so severe as to preclude sufficient gonadal function for conception.

The anemia occurring in hypopituitarism has been studied by Summers (103). Experimentally the anemia is not improved by the administration of growth hormone, although it is reported to be aided by cobalt (104). The anemia of adenohypophyseal insufficiency is usually macrocytic or normocytic and hypochromic in type. In a series of 10 cases studied, iron, liver, thyroid, and testosterone were without effect. In the two instances in which cortisone was employed a prompt increase in the hemoglobin and the number of red blood cells was obtained. In a series of patients with chromophobe adenomas of the pituitary with anemia reported by Younghusband *et al.* (117) somewhat similar results were noted.

The most important recent therapeutic measures in the treatment of hypopituitarism have been the use of cortisone and ACTH. Favorable results have been observed by us and by others both in the day by day management of the patients and in the treatment of hypopituitary crisis and coma (105 to 109). In the latter, the use of glucose to control whatever hypoglycemia is present is essential. Nevertheless, as in adrenal crisis, sudden death may still occur in the patient with severe hypopituitarism in spite of attempts at correction of known and recognized metabolic abnormalities. Sheehan & Summers (105) have summarized the clinical manifestations of coma in hypopituitarism: it may follow a minor stress or infection; the patient becomes drowsy, stuporous, and then comatose, often preceded by convulsions; she may be rigid, or flaccid and unresponsive; the heart sounds are almost inaudible, the pulse is impalpable, the nose and extremities are cold and dry, the face is pale, and hypothermia is often present. Dramatic results may at times be obtained simply by raising the body temperature with hot packs or warm baths.

Surgical hypophysectomy in patients.—Surgical hypophysectomy (95) has been introduced in the treatment of malignant disease. Shimkin and co-workers (110) reported such a procedure, which was without effect on a patient with a malignant melanoma. The post mortem examination revealed atrophy of the testis, thyroid, and adrenal cortex. During the nine-week postoperative course the patient gradually developed the clinical picture of

hypopituitarism. Clinical changes were noted within two weeks after stopping substitution therapy and four weeks after the operation. Further work with hypophysectomy in the treatment of carcinoma will probably be undertaken in view of the experimental production of tumors with growth hormone and the report of the inhibition of methyl cholanthrene carcinogenesis by hypophysectomy (112).

Chromophobe adenomas.—Younghusband *et al.* (117, 118) reviewed their experience in the diagnosis and treatment of chromophobe pituitary tumors. Their material consisted of 164 presumed cases, of which 105 were verified histologically. The presence of enlargement of the sella turcica and signs of hypopituitarism make the diagnosis likely. The additional presence of primary optic atrophy and bitemporal visual field defects render the diagnosis almost certain. It is to be borne in mind that many lesions can produce enlargement of the sella. These include chromophobe, mixed and eosinophile tumors, suprasellar tumor, craniopharyngioma, aneurysm of the internal carotid artery, cretinism, increased intracranial pressure of varied etiology, or intracranial tumors distant from the sella turcica. Occasionally, enlargement of the sella turcica is encountered in females castrated before the age of 25. Chromophobe adenomas may produce marked visual field defects without gross endocrine disturbance. Chromophobe adenomas constituted 7.1 per cent of all their intracranial tumors and represented 86.8 per cent of all pituitary adenomas studied at their clinic. These tumors are usually benign, although rare malignant ones have been reported. They may grow upwards, or downwards, or laterally, producing varying symptoms. They may be cystic. In the series reported by the above authors, the largest age group was between 30 and 60 years. In some, symptoms had been present for over 10 years before help was sought. The sex incidence was approximately equal. The clinical signs and symptoms were due either to increased intracranial pressure or to hormonal insufficiency or both. Visual disturbance was present in 80 per cent of the patients. Headache was present in 67 per cent. Other symptoms included drowsiness, stupor or coma, insomnia, convulsions, personality changes, impaired memory, and visual hallucinations. The endocrine features varied from their total absence to the presence of severe panhypopituitarism. At times the picture resembled that of failure of either the thyroid, the adrenal cortex, or the gonad. By and large, the endocrine signs and symptoms and the laboratory findings were those found in hypopituitarism.

The treatment of choice consists of x-ray irradiation of the pituitary. If visual impairment progresses or ensues, or if the tumor is extensive, an attempt at surgical extirpation is indicated, followed by pituitary irradiation. There was an over-all death rate of 14.1 per cent following surgery. Of the 68 survivors, 49 lived 5 to 18 years, 6 at least 1 to 4 years, 11 died within 5 years, 6 of these from recurrence and 5 from other causes. By and large, 67 per cent were benefited by treatment for an average period of $5\frac{1}{2}$ years. Surgical intervention or pituitary radiation were helpful in a large majority of instances in maintaining or improving vision but had no effect on the endocrine mani-

festations. The treatment of the latter consisted of specific end organ replacement therapy, with emphasis on cortisone and ACTH. Aitken & Pohle in a similar report emphasized the favorable results obtained with pituitary irradiation (119, 139).

The neural control of the adenohypophysis.—Harris (122) reviewed the evidence for neural control of the adenohypophysis through the hypothalamus. He believes such pathways exist and that the humoral control is exerted through the hypophyseal-portal system. He points out that following hypophysial grafts to the eye or spleen there ensues atrophy of the target end organs (122, 128). Some functional integrity undoubtedly remains, since stress induces a fall in the circulating eosinophiles and in the adrenal ascorbic acid (123, 124, 130). However, when the hypophyseal stalk is sectioned (131, 137) or grafts are placed in apposition to the cut ends of the hypophyseal-portal system, revascularization of the vascular bed occurs, and the functional integrity of the cut or grafted adenohypophysis is maintained, as is evidenced by the normal size and function of the target end organs. According to Harris, evidence favors the hypothalamic control of both gonadotropin and ACTH, although control of the latter is probably dual, being both humoral and neurohumoral. Scow & Greer (125) implanted the pituitary in the eye of the hypophysectomized mouse. The uptake of I_{131} by these mice was two-thirds of that observed in the intact animals per unit of thyroid weight. Although the administration of thyroxin reduced the thyroidal uptake of I_{131} in both implanted and intact animals in comparison to that of the hypophysectomized mice, the administration of propylthiouracil did not increase the thyroid weight in the former as it did in the latter animals. These findings perhaps suggest that Harris' explanation might hold similarly for the regulation of thyrotropin secretions. Indeed, Greer (128) has suggested that the adenohypophysis secretes both a thyroid "growth factor" and a "metabolic factor," the former being dependent on direct contiguity of the hypothalamus for its secretion and the latter being independent of hypothalamic control. Of some interest is the observation of Jensen & Clark that radioactive thyroxin is concentrated in the median eminence and pars nervosa of the pituitary gland (129). More recently, studies have been initiated by Slusher & Roberts (126) in an attempt to demonstrate the existence of pituitary-stimulating activity in fractions obtained from the hypothalamus.

Bauer (127) has studied the endocrine and clinical manifestations of hypothalamic disease in 60 cases subjected to post mortem examination. A high incidence of gonadal dysfunction was found, 24 exhibiting precocious puberty, and 19 showing evidence of depressed gonadal functions. The basal metabolic rates were frequently low. Other clinical manifestations included those usually associated with diencephalic disease, such as obesity, somnolence, and diabetes insipidus.

THE NEUROHYPOPHYSIS

Harris (121) has reviewed the neural control of the neurohypophysis. He again emphasized the view that following interruption of the supraoptic-

hypophyseal nerve tracts, the neurohypophysis atrophies, its secretory activity ceases, and diabetes insipidus frequently follows. Excitation of the intact gland can be provoked by hypertonic saline, emotion, nicotine, acetylcholine, and by direct electrical stimulation. It is not certain whether the antidiuretic and oxytoxic principles are one or multiple hormones. There is evidence for both views. In any event, the latter fraction is probably the factor concerned with milk ejection (14, 121), although Whittlestone (9) has found some milk-ejecting factor associated with Du Vigneaud's purified vasopressin.

Van Dyke (132) reviewed the regulation of water excretion by the neurohypophysis. He pointed out that the adult human pituitary contains approximately 15,000 milliunits (m.u.) of antidiuretic hormone (133) and that 7.5 to 50 m.u. per hr. are ordinarily required by man (134). A detectable effect can be obtained by the intravenous administration of as little as 0.5 to 2 m.u. The polypeptide prepared by Turner and associates (135), containing only eight amino acids, has an antidiuretic potency of at least 600,000 m.u. per mg. The list of drugs exciting the discharge of antidiuretic hormone includes ether, phenobarbital, dimercaprol, yohimbine, nicotine, 3-hydroxy-2-phenyl cinchoninic acid and related compounds, and ferritin (136).

Leaf *et al.* have investigated the role of the other endocrine glands in diabetes insipidus (140, 141, 142). A patient with diabetes insipidus who subsequently developed adenohypophyseal failure was the subject of the study. These authors reported that the beneficial effect on the polyuria and polydipsia following the loss of adenohypophyseal function was a result of the subsequent decrease in excretory solute load. If the solute load were maintained constant, the administration of thyroxin, desoxycorticosterone, cortisone, corticotropin, and growth hormones was without effect on water excretion. The possibility that these agents might in some fashion interfere with the release or action of antidiuretic hormone was not excluded. The intrinsic defect in diabetes insipidus, namely an inability to elaborate a concentrated urine in response to increased serum solute concentration, persisted in the patient despite the absence of polyuria. In another study (141), however, cortisone was shown not to interfere with the release of antidiuretic hormone, since patients with Addison's disease treated with Compound E were capable of excreting a concentrated urine.

The role of the antidiuretic hormone in the retention of water associated with heart failure, cirrhosis of the liver, and other clinical syndromes has been the subject of several investigations. White *et al.* (145) and Nelson & Welt (146) failed to observe any differences in effect following the administration of moderate doses of beta-hypophamine (Pitressin) to normal, hydrated, and cirrhotic subjects. With larger doses, some delay in the recovery from the antidiuresis was noted. Bernstein and associates (139) observed a satisfactory antidiuretic response to nicotine and beta-hypophamine in a majority of their patients with hepatic cirrhosis with varying degrees of ascites. These studies suggest that in cirrhosis of the liver there is

neither hypersecretion nor impaired inactivation of antidiuretic hormone, nor is there any evidence to suggest increased renal tubular sensitivity to this fraction.

In view of the reports of increased antidiuretic activity of the urine from patients with cirrhosis, certain noncardiac edematous states and congestive heart failure, Perry & Fyles (138) attempted to determine the serum level of antidiuretic hormone in patients with such disorders, employing the method of Birnie *et al.* (147). They noted that human serum did contain a labile substance that was antidiuretic in character but differed from antidiuretic hormone from the posterior pituitary in being nonchloruretic. No significant deviation from the values observed in the sera of normal individuals was seen in patients with congestive heart failure or liver disease. They concluded therefore that the retention of fluids in these states did not result from alterations in the serum level of antidiuretic activity. It is interesting in this regard that an increase in the urinary excretion of a salt-retaining fraction, possibly associated with the adrenal "amorphous" fraction of Kendall, has been reported in the urine of patients with cirrhosis of the liver with ascites but was not found in patients with cirrhosis but without ascites (148).

Stein *et al.* have reviewed the methods employed in the past for assaying antidiuretic hormone and have suggested a new method said to be more precise, convenient, and economical (149). With this method they observed a measurable quantity of antidiuretic substance in the plasma of normal subjects ($\backsim$ 15 to 60 m.u. beta-hypophamine/100 ml.).

Heller reported that vasopressin is much less effective in newborn rats than in the adult, indicating that for some time after birth the kidney is less responsive to this fraction than in adult life (150). This would complement his previous report concerning the marked decrease of antidiuretic principle in the neurohypophysis of the infant rat compared to that of the adult.

A case of diabetes insipidus associated with hyperthyroidism and treated with I_{131} was recently reported. The treatment resulted in the amelioration of both conditions, again illustrating that some instances of diabetes insipidus may be improved following medical or surgical thyroidectomy (143).

Four interesting cases of pulmonary disease associated with diabetes insipidus, reported by Spillane (144), point up the fact that a fortuitous juxta-hypothalamic lesion of a generalized disease may result in diabetes insipidus. The cases reported were those of Boeck's sarcoidosis, xanthomatosis, and eosinophilic granuloma.

The Adrenals

Chemistry and physical properties of corticotropin.—The chemistry and physical properties of ACTH have been reviewed in great detail by Li (10, 157), by Astwood *et al.* (152), and by Dedman and co-workers (153). Although Li had felt that the protein isolated by him and his group in 1942,

and independently by Sayers and associates (158), was a purified adreno-corticotropin, recent studies suggest this is probably unlikely. The protein was homogenous and had a molecular weight of 20,000. From this homogenous protein Li was able to prepare active peptide fragments by partial hydrolysis. These peptide fragments had greater metabolic activity than did the original starting protein. The molecular weight of one of these peptides (S) prepared by peptic digestion was 1200. Evidence was adduced by Li that more than one such active peptide, of varying molecular weights, exist. In an addendum to his Harvey Lecture (10) Li concedes that more recent evidence would suggest that the original ACTH preparation was probably not entirely pure, since it is in part dialyzable, and that a hormone can be obtained from it with a molecular weight of approximately 10,000. Acid and peptic hydrolysis of this fragment did not cause a loss of the ascorbic acid depletion potency, suggesting that the activity might reside in a peptide fragment. The data reviewed by Astwood (152) and Morris (see 153) suggest that as yet no completely pure form of this hormone has been isolated. It seems likely that ACTH is a water-soluble, nonvolatile organic compound of modest size and basic properties. It apparently is of peptide nature and is easily adsorbed onto a variety of substances. It is probable that there is no free alpha amino group, but that one or more carboxyl groups and one or more amino groups are essential to its activity. Until purified preparations are obtained, doubts will continue to be present as to whether the described chemical and physical properties are those of the active hormone or of possible contaminants.

It is unfortunate that the biological potency of any given ACTH preparation varies with the mode of assay, and that different assay methods do not necessarily yield similar potency values (157, 160, 344). The commonly accepted methods employed include adrenal hypertrophy; repair and weight maintenance; adrenal ascorbic acid and cholesterol depletion tests; measurement of the blood levels of adrenal cortical steroids and the indirect effects exerted by these steroids on the blood level of circulating eosinophiles and lymphocytes; and, finally, the involution of the thymus and lymph nodes. In human assays, varying degrees of inactivation have been observed when ACTH has been administered by the intramuscular route, although such inactivation does not occur following intravenous administration. As a consequence, it has been postulated that more than one ACTH may exist (154, 155, 343).

An assay method for corticotropin based on the reduction in thymus weight in nestling rats has recently been suggested by several groups of investigators (323, 382). This principle has been used clinically by Soffer, Gabrilove & Wolf (383) in the treatment of thymic masses.

Incubation of ACTH protein or polypeptide with liver, kidney, or adrenal homogenates results in inactivation of the hormone. The degree of inactivation is reduced if the tissues are previously boiled. It has been suggested that the inactivation is due to adsorption of the active fraction onto the tissue.

Geschwind & Li found no inactivation of corticotropin after incubation with rat plasma (345). Polyphloretin-phosphate will protect ACTH against inactivation in tissue homogenates and will delay its adsorption, while polyvinylpyrrolidone does only the latter (253). Alum precipitation has been found to enhance ACTH activity in the rat (171).

ACTH assay in blood (261).—Farrell & McCann (159) assayed the blood ACTH content in intact control and epinephrine-treated animals by injecting plasma into recipient hypophysectomized rats. They reported the presence of 0.026 milli unit/cc. of ACTH in the blood of intact rats and 0.064 milli unit/cc. in epinephrine-treated animals. The administration of epinephrine in human subjects, however, failed to increase the blood level of the 17-hydroxycorticoids (249). Sydnor & Sayers (235), using an oxycellulose technic for blood assay of corticotropin, found values as follows: decapitated normal rats <1.1 milli unit/100 cc.; exsanguinated rats 2.5 milli unit; adrenalectomized rats 11. 1milli unit; normal human males <1 milli unit; male patients with Addison's disease 2 to 4 milli unit/100 cc. In another study the parenteral administration of epinephrine in adrenalectomized animals has been reported to decrease the anterior pituitary content of ACTH and to lower the blood concentration of this hormone (250).

Intermedin and the melanophore hormone. —It has been known that a hormone affecting melanophores is present in the pituitary of both cold blooded animals and many vertebrates. More recently it was suggested that the melanophore hormone and ACTH might be identical. This has been based inferentially on the following lines of evidence: (*a*) the suggestion that melanin synthesis is controlled by melanophore hormone; (*b*) the occurrence of pigmentation (melanin) in patients with Addison's disease and in individuals treated with ACTH; (*c*) the finding of an increased amount of melanophore hormone in the blood of patients with Addison's disease and a decrease in melanophore content of the blood following treatment with cortisone; (*d*) correlation of the melanophore test and the ascorbic acid depletion test in various crude and purified ACTH preparations (161, 162, 264). Sulman has suggested that the chromatophore test be employed as a method of ACTH assay. He points out, however, that the chromatophore response is considerably reduced when ACTH polypeptides are employed (163). Methods have been described for assay in *Hyla arborea* (163) and the larvae of *Xenopus laevis* (164). Li is skeptical of the value of chromatophore assays for ACTH content since the effective separation of intermedin from corticotropin (157, 346, 347, 387).

Adrenal cortical steroid synthesis.—The synthesis of the adrenal cortical steroids has been reviewed by Hechter *et al.* (165, 170) and by Haines (166). Both groups have shown that the adrenal steroids can be derived from acetate as well as from cholesterol, and that the action of ACTH is probably on the intermediary steps between cholesterol and pregnenolone or perhaps at an earlier stage. They further found that the adrenal possesses mechanisms for hydroxylating at the 11, 17, and 21 positions even in the absence

of corticotropin. The essential steroids produced by the perfused adrenal gland are cortisone and 17-hydroxycortisone. More recently, biological methods independent of the adrenal have been developed for the hydroxylation at the C11 position (390, 391).

Simpson & Tait (173) have described a sensitive method for the bioassay of corticosteroids on mineral metabolism employing the effect on the Na^{24}/K^{42} ratio in adrenalectomized rats. An assay method employing only Na^{24} has also been described (174). Using the former technic, Tait *et al.* isolated a fraction previously unknown which exerted a profound sodium-retaining effect, perhaps 25 times greater than that of desoxycorticosterone (175, 176). They suggest that this fraction may reside in the amorphous residue of the adrenal gland. Luetscher *et al.* have studied the sodium-retaining activity of the urine of edematous patients and subjects on a low sodium diet and, in the latter group, identified a mineral corticoid resembling that described by Grundy, Simpson, Bush, and Tait (see 348).

Nelson & Samuels described a process for the estimation of the 17-hydroxycorticoids in blood. This method employs chromomatographic separation after extraction and partition of blood, and the final quantitative determination by a modification of the Porter-Silber (238) color reaction. Normal values of 4 to 10 γ per cent were found. Increased values were obtained after ACTH administration (168, 237, 248, 249, 388, 389). Total body irradiation of dogs resulted in a marked increase in the blood content of these fractions (236).

Effect of adrenal cortical steroids on water and electrolyte metabolism.—An interesting study was conducted on the course of experimental adrenal cortical insufficiency in the rhesus monkey. The findings were for the most part similar to those observed in man. The blood nonprotein nitrogen, inorganic phosphorus, and serum potassium rose, while there occurred a decrease in the blood glucose, serum chloride, and serum sodium levels. The blood amino acid nitrogen was initially increased and then fell. The hematocrit fell sharply postoperatively and subsequently returned to a normal level before death (191).

In short acute experiments Bloodworth (187) found that the administration of adrenal cortical extract to the intact dog produced an increase in the extracellular compartment, although the total body water remained constant. Corticotropin and desoxycorticosterone acetate failed to induce similar changes. Sjögren reported that cortisone and desoxycorticosterone acetate initially induce a retention of sodium and later a diuresis of this ion (255, 258). These results are of interest in view of the findings of Levitt & Bader (256) that the administration of ACTH and cortisone to patients produces a temporary expansion of the extracellular compartment even on a salt-free diet. These findings are of some interest as a possible explanation for the phenomenon of salt diuresis which often follows the administration of desoxycorticosterone acetate to patients with Cushing's syndrome (257). An extended observation of the effects of desoxycorticosterone acetate in

the human subject was reported by Luft & Sjögren (258). These authors suggest that desoxycorticosterone acetate may mobilize sodium from bone (258), since the urinary excretion of calcium and phosphorus is markedly increased during treatment. Ulrich and co-workers (259) demonstrated that in the rat ACTH increases the urinary and fecal excretion of Ca[45]. Similar results are obtained in the human subject (260). In young rats, adrenalectomy stimulates epiphyseal growth and retards periosteal bone formation (384). Desoxycorticosterone acetate inhibits epiphyseal and periosteal growth, as well as body and tail growth, in normal young rats and interferes with the action of growth hormone on tail growth in the hypophysectomized rat (116, 259).

It is well-established that the hypophysectomized as well as the adrenalectomized rat displays an impaired ability to excrete a test load of water. Hofman reports that adrenalectomy further reduces the impaired tolerance to water loading in the hypophysectomized rat, adding additional evidence for the concept of some degree of autonomy of adrenal cortical function in this species (188). Following hypophysectomy in the dog there occurs a decrease in the glomerular filtration rate and renal blood flow that can be partially corrected by the administration of growth hormone (192), while ACTH and adrenal replacement therapy are without effect (193). In the hypophysectomized rat adrenal cortical extract exerts little effect on the impaired renal clearances but does improve the functional activity of the tubules, as is evidenced by a decrease in the tubular reabsorption of water, an increase in the urine flow, and total electrolyte excretion (194).

Warming-Larsen et al. (254) suggest the use of the sodium concentration of saliva following the injection of pilocarpine as a simple test of adrenal cortical function with regard to salt regulation. The comparative simplicity of the method would suggest its use in lieu of the sweating test. These observers find that the determination of the Na/K ratio in saliva is not essential for the specificity of the test.

In adrenal insufficiency there is a decrease in the rate of glomerular filtration and renal plasma blood flow. The administration of desoxycorticosterone restores these functions to normal levels (189). Roberts & Pitts (190) find that in the adrenalectomized dog cortisone acts similarly to desoxycorticosterone acetate in these respects. They suggest that the changes in potassium levels observed in treated and untreated adrenal insufficiency are partly due to primary derangements of potassium metabolism rather than secondary to the renal excretion of this ion. The effects of the adrenal steroids appear to be in part on the correction of the loss of extracellular fluid volume and lowered serum sodium with concomitant changes in renal hemodynamics.

The role of the adrenal in hypertension.—In the rat, Compound F (17-hydroxycorticosterone) has been found to be a more hypertensive agent than desoxycorticosterone acetate (195). Compound S (11-desoxy-17-hydroxycorticosterone) is qualitatively similar but quantitatively less potent than

desoxycorticosterone. Hypertension as well as similar pathologic changes on the cardiovascular system and the kidney can be produced, but this fraction exerts no effect on thymus weight (386). Masson *et al.* (196) reports that cortisone potentiates the hypertensive effect of desoxycorticosterone acetate. However, Hall & Hall find that hypertension occurring in parabiotic rats is abolished by cortisone prior to the development of severe arterial lesions (197).

In man, adrenal cortical extract has been reported tp prevent the hypertensive effect of desoxycorticosterone (198), while cortisone inhibits the development of the cardiac and renal lesions produced by desoxycorticosterone in rats (199, 232). It has been suggested that this inhibitory effect of cortisone is due to its inhibition of inflammatory reaction (232).

Hetzel and co-workers (227) have been unable to find any evidences of increased adrenal cortical function in human hypertension. They used as indices the urinary excretion of the neutral 17-ketosteroids and the glucocorticoids.

The role of the adrenal in nitrogen metabolism.—Engel studied the relation of adrenal cortical function to stress and nutrition with particular reference to nitrogen metabolism (216, 217). This author suggests that the adrenal cortical hormones condition the organism to respond to stress with a characteristic metabolic pattern. Adrenal hormone is necessary but not responsible for the nitrogen metabolic response. Provided that adequate hormone is present, the magnitude of the stress rather than the amount of adrenal hormone determines the protein catabolic response. It is of interest that the nitrogen loss induced by ACTH or cortisone decreases after several days, particularly when food intake increases, suggesting that nutritional as well as other factors are involved in the nitrogen response (217, 352, 353).

The role of the adrenal in carbohydrate metabolism.—Nichols & Sheehan (212) conducted illuminating studies with 2,2 bis(para-chlorophenyl)-1,1-dichloroethane (DDD), a compound which previously had been noted to cause atrophy and disappearance of the inner two-thirds of the adrenal cortex, leaving the zona glomerulosa intact (213). Dogs treated with this compound failed to develop diabetes when alloxan was subsequently administered, and the electrolyte balance remained satisfactory (212). It is of interest to compare the effects of this compound with those of amphenone B. Amphenone B, which has progestational activity in the rabbit and a folliculoid effect in the castrated female rat, induces thyroidal hyperplasia and adrenal hypertrophy in the rat (74). The goitrogenic effect can be suppressed by thyroxin, and the adrenal effect by cortisone. In further studies Hertz *et al.* (215) found that concomitant with the adrenal hypertrophy there occurs an increase in the adrenal cortical concentration of cholesterol. Following stress, animals so treated exhibit a fall in adrenal ascorbic acid but no change in the gland cholesterol concentration takes place. Glutathione, in a manner as yet unknown, protects the experimental animal against diabetes induced by alloxan or dehydroascorbic acid but potentiates steroid diabetes in the rat (351, 354).

Ingle studied the effect of various forms of stress on the force-fed adrenalectomized rat treated with a constant amount of adrenal extract. In such animals some agents such as diethylstilbestrol are diabetogenic, while formalin decreased the glycosuria. He also found that ethylenediamine was diabetogenic in the intact, but not in the adrenalectomized rat. He concluded that the adrenal cortex is probably not entirely responsible for the metabolic effects of stress on carbohydrate metabolism (219).

The role of the adrenal in fat metabolism.—The role of the adrenals in fat metabolism is still largely unresolved. The suggestion that cortisone interferes with fatty acid synthesis has received some recent support (355), but this view apparently is not entirely acceptable (356, 357).

The administration of cortisone to the rabbit is followed by some increase in the serum lipoprotein of the 80 to 400 class, and following cessation of treatment conversion of these fractions to those of the normal Sf 3 to 12 class takes place (358). However, no effects were noted on the lipoproteins in human subjects (359).

Adrenal-thyroid relationship.—Ever since the effect of stress and of cortisone on the uptake of radioactive iodine by the thyroid gland of the rat was originally described by us (200, 201) investigations have been carried out in many laboratories in an effort to determine whether this effect is induced by the inhibition of the secretion of thyrotropin or by interfering with the action of this fraction on the thyroid gland. Among the evidence against the inhibition of TSH secretion is the finding that cortisone does not decrease the rate of discharge of I_{131} from the thyroid, a function known to be under TSH control (207, 208).

Migeon *et al.* (202) found that cortisone decreases the thyroidal uptake of I_{131} in adrenalectomized rats treated with desoxycorticosterone but not in intact rats. In none of the groups was there a difference in the proportion of I_{131} in the thyroxine, mono- or diiodotyrosine, or inorganic iodine fraction. The adrenalectomized rats maintained on desoxycorticosterone and treated with cortisone showed an early increase in I_{131} concentration in the blood, but a decreased excretion in the urine and feces. Boatman and associates (206) have pointed out that desoxycorticosterone apparently causes increased retention of I_{131} by most tissues.

Halmi & Barker (203, 204) studied the effects of cortisone on the histology of the rat hypophysis and thyroid and on the level of the protein-bound iodine in the plasma and in the thyroid gland. No effect was noted that could be correlated with a decreased output of ACTH. There was histological evidence of increased TSH secretion and corresponding hyperactivity of the thyroid body, The thyroid content of protein-bound iodine, however, was low, while the serum protein-bound iodine was increased. Halmi (204) further observed that, contrary to the findings of Woodbury *et al.* (205) and of Verzar & Vidovic (266), cortisone does not prevent the histologic effects of exogenous TSH administration on the thyroid.

Berson & Yalow (229) reviewed the clinical effects of ACTH and cortisone on I_{131} metabolism. They observed that the administration of cortisone to

the human subject results in a decrease in the thyroidal accumulation and an increase in the renal clearance of I_{131} (229, 231). The serum protein-bound iodine is decreased after massive cortisone treatment (230). In this latter study the comcomitant administration of TSH and cortisone resulted in an increase in the thyroidal accumulation of I_{131}.

Adrenal and gonads.—Gemzell showed that the parenteral administration of estradiol benzoate to rats increased the secretion of ACTH (252). On the other hand, following surgical stress (370) or the administration of cortisone or ACTH the urinary excretion of gonadotrophins is often increased (371).

Relation of adrenal corticoids to ascorbic acid.—Bacchus and associates, in a series of experiments, have reported that ascorbic acid prevents the peripheral blood eosinophile decrease after epinephrine but not following the administration of ACTH, that it potentiated the gluconeogenic and hematologic effects of cortisone, and that it decreases the urinary excretion of the neutral 17-ketosteroids following therapy with this fraction. They presume that ascorbic acid acts to decrease the inactivation of the glucocorticoids (178, 180, 181, 182, 263). They suggest that the adrenal hypertrophy (179, 184) and increased excretion of cortical hormone metabolites in scurvy is due to the absence of ascorbic acid and the consequent failure to maintain the circulating level of hormones. In any event, ascorbic acid does not appear to be necessry for adrenal cortical hormone production (179). Herrick *et al.* (183) find that the administration of cortisone results in adrenal atrophy in scorbutic guinea pigs. In human subjects, Kazahan (263) found that the administration of ascorbic acid resulted in a decreased urinary excretion of the neutral 17-ketosteroids and an increased excretion of the 11-oxygenated steroids. The intravenous administration of ascorbic acid to patients receiving cortisone results in a more prolonged and higher blood level and a decreased urinary excretion of ascorbic acid (228).

The adrenal cortex and pantothenic acid.—Marked histological alterations of the adrenal, particularly of the zona fasciculata and the zona reticularis, occur in the pantothenic acid-deficient rat. Such animals are sensitive to water intoxication and fail to respond to ACTH or epinephrine as demonstrated by a lack of effect on the peripheral blood eosinophile and lymphocyte counts (185). The hemorrahgic necrosis of the adrenals in pantothenic acid-deficient rats can be prevented by cortisone and exacerbated by ACTH (186). It is suggested that a functional adrenal cortical insufficiency develops as a result of the depletion of coenzyme A (186).

The effect of adrenal steroids and of ACTH on the peripheral blood cells.— It is well established that the circulating eosinophiles decrease following stress, the administration of ACTH, and after the use of cortisone. It has been suggested that the mechanism is (a) an actual inhibition of formation and release of the cells from the bone marrow; (b) a redistribution of the cells; or (c) destruction of the eosinophiles. Padawer & Gordon (209) have reviewed the experimental aspects of the problem and offer evidence for the hypothesis that the eosinophiles are destroyed under these circumstances. Similar find-

ings are reported by Godlowski (262). Of collateral interest is the finding of Hull & White (210) that the reduction in turnover of P_{32} following injection of ACTH is a reflection in part at least of the inhibition of mitosis of lymphocytes.

Tests of adrenal cortical function.—Thorn *et al.* (220) have previously proposed the eosinophile response to ACTH as a diagnostic test for Addison's disease. They conclude that a fall of 50 per cent or more in the absolute number of the eosinophiles in the peripheral blood 4 hr. after the injection of 25 mg. of ACTH eliminates the diagnosis of adrenal cortical insufficiency, whereas a fall of less than 50 per cent may suggest the possible presence of adrenal cortical insufficiency. They also suggest a similar test employing epinephrine to estimate the functional activity of the pituitary-adrenal axis (221). A statistical analysis of these tests was reported by Best and associates (222), and these authors found that: (*a*) one-sixth of all patients given placebos showed an eosinophile reduction greater than 50 per cent; (*b*) one-sixth of all nonaddisonian patients given corticotropin had an initial eosinophile fall of less than 40 per cent and almost one-third less than 50 per cent; (*c*) on subsequent retesting, these latter patients now demonstrated a greater than 50 per cent fall; (*d*) no instance was known to the authors of a patient with Addison's disease who developed a significant eosinopenia following the use of ACTH; (*e*) in patients who were maintained on cortisone following adrenalectomy, a significant fall of eosinophiles was observed after the administration of epinephrine (322); (*f*) half of a group of normal individuals tested had less than a 50 per cent fall in eosinophiles following the administration of epinephrine. These authors and others conclude that the use of epinephrine as a test of adrenal cortical function is of little value. Repeated failure of response to ACTH is suggestive of Addison's disease (242, 243). The intravenous administration of ACTH, introduced originally by Gordan (233), affords maximal stimulation of the adrenal with smaller quantities of corticotropin. Thorn finds that in normal subjects, after an 8 hr. infusion of 15 to 20 mg. of ACTH there is a fall of 80 per cent or more in the circulating eosinophiles at the end of the tenth hour, while in patients with Addison's disease a fall of only 30 per cent or less is observed. He suggests the simultaneous measurement of the urinary excretion of the neutral 17-ketosteroids (223, 224, 234). Nelson and co-workers (249) found that the administration of epinephrine to normal human subects failed to produce any increase in the blood level or urinary excretion of the 17-hydroxycorticoids or the urinary excretion of the neutral 17-ketosteroids, nor did epinephrine influence the rate of disappearance of Compounds E or F from the blood of normal subjects of patients with Addison's disease. No evidence was found to suggest that epinephrine stimulates the secretion of adrenal cortical steroids or modifies the peripheral utilization of these compounds. They suggest that epinephrine may perhaps potentiate the action of the 17-hydroxycorticosteroids.

Soffer & Gabrilove (271) have described a simplified water-loading test

for the diagnosis of adrenal insufficiency. The fasting patient is given orally 1500 cc. of water, and the urine volume is measured over a 5 hr. period. Normal subjects excrete 1200 to 1900 cc., while patients with Addison's disease or with hypopituitarism and adrenal insufficiency excrete less than 800 cc. These results have been confirmed by Oleesky (272), and the test warrants further trial.

A simplified procedure has been reported for the determination of the urinary neutral 17-ketosteroids employing ethylene dichloride as a solvent (225), and amyl acetate has been used to improve the final Zimmerman color reaction (244). Employing a chromatographic technic for the analysis of the urinary neutral 17-ketosteroids, Dingemanse and co-workers (226) find that normal women excrete 1.5 to 20 mg. and normal men 9.4 to 30.6 mg. in 24 hr. Rubin et al. (247) have described a new method for separation of the urinary 17-neutral ketosteroids.

Plate (251) administered large amounts of chorionic gonadotropin to two female castrates and one eunuchoid male. A marked increase in urinary excretion of the 17-neutral ketosteroids was observed, suggesting stimulation of the adrenal cortex.

Employing the Porter-Silber method for the determination of the urinary excretion of 17,21,dihydroxy-20-ketosteroids, Carroll and associates (239) found that normal male subjects excrete 0.1 to 0.4 mg. per 24 hr., and female subjects 0.0 to 0.86 mg. Krupp et al. (240) found no urinary excretion of these compounds in normal subjects, but they probably used a less complete extraction method. These latter investigators found urine values up to 5 mg. per 24 hr. in subjects given as much as 200 mg. of cortisone or Compound F by mouth, but none if the adrenal steroid was administered intramuscularly. The administration of ACTH intravenously was followed by a marked increase in the urinary excretion of the 17,21-hydroxy-20-ketosteroids as well as of the neutral 17-ketosteroids.

Ketosteroids in adrenal cortical tumors.—Seligman & Ashbel (218), employing a histochemical method for staining active carbonyl groups, studied 15 nonvirilizing tumors of the adrenal cortex. Of these, six were associated with Cushing's syndrome. They found that in Cushing's syndrome the reactive groups were present unless prolonged fixation had leached the water soluble compounds. On the other hand, lipid soluble fractions, such as are found in virilizing adrenal cortical tumors, remained in spite of prolonged fixation. They believe the stained carbonyl groups represent the glycogenic corticoids (water soluble) and the 17-ketosteroids (lipid soluble).

Addison's disease.—Some interesting etiological causes for Addison's disease have been reported. They include disseminated coccidiomycosis (274), metastatic carcinoma (275, 276), suprarenal hemorrhage (329), and adrenal cortical necrosis occurring during pregnancy (277, 284). Six more instances of Addison's disease in the negro were reported by Tucker et al. (278). The incidence in negroes in their series suggests that it occurs with approximately the same frequency as in whites.

Schwartz and colleagues (279) reviewed the risk of anesthesia and surgery in patients with Addison's disease. The hazard involved is still considerable, although with current therapy the risk has been reduced. This problem, as well as the management of complicating disease such as heart failure, is of increasing seriousness in view of the current therapeutic use of bilateral adrenalectomy.

Gaunt and co-workers (280) and Swingle and his group (341) studied the effects of various desoxycorticosterone esters and found the trimethylacetate to be superior to the others in its length of action. Clinical use of this agent in the treatment of Addison's disease has been made by Thorn (111) and by us (156). Forty to sixty mg. of the microcrystals of this ester will afford replacement therapy for approximately four to six weeks.

Swingle *et al.* (342) observed that the water soluble glucoside of desoxycorticosterone was quite effective in the treatment of dogs with adrenal insufficiency and crisis when given intravenously. It is of interest that crude licorice was reported to be of value in retaining sodium and chloride and correcting the physiological defects of Addison's disease (281, 336).

Cushing's syndrome.—A report dealing with the treatment of 33 patients with Cushing's syndrome has recently appeared (285, 286). Of this group, 19 patients were treated with pituitary irradiation. A complete remission was obtained in three instances, and in six some improvement resulted. Adrenal irradiation, used in two patients, was without effect. Seventeen patients were operated upon. Of the five from whom a benign tumor was removed, three died postoperatively and the remaining two were cured. Removal of a carcinoma resulted in temporary improvement, but death subsequently resulted from metastases. Of the 11 patients with cortical hyperplasia, 10 had bilateral partial resection and one had unilateral subtotal resection. One patient died postoperatively and one improved.

The poor prognosis associated with unsuccessful treatment of this disease is emphasized by the fact that 17 patients died within five years of the onset of the illness. In a review of 114 cases collected from the literature, the usual causes of death were infection, cardiovascular disease, and neoplastic metastases.

Walters (297) reviewed the experience of the Mayo Clinic with subtotal adrenalectomy for Cushing's syndrome. Of 29 patients thus treated, 6 died and 19 have had excellent remissions. Three of the latter group subsequently developed Addison's disease. Three other patients had recurrence of symptoms after intervals of nine months, two years, and three years.

The urinary excretion of the neutral 17-ketosteroids in Cushing's syndrome has been reviewed by Forbes & Albright (292). In general they found the average daily urinary excretion in 90 cases to be as follows: (*a*) in the absence of tumor 18.1 mg. per 24 hr.; (*b*) with benign tumor 5.7 mg. per 24 hr.; and (*c*) with malignant tumor 124.4 mg. per 24 hr. Adrenal cortical hyperfunction due to a benign adrenal cortical tumor is usually associated with a low urinary excretion of the neutral 17-ketosteroids, bilateral hyper-

plasia with a moderately increased excretion, and malignant tumor with a markedly increased excretion. Migeon & Gardner (295) found the urinary estrogens to be increased in one patient with Cushing's syndrome due to an adrenal cortical carcinoma, but no increase occurred in three patients with adrenal hyperplasia.

In an analysis of 53 proven cases of Cushing's syndrome personality changes were observed in 60 per cent. These included severe depressions, psychotic episodes, irritability, mental retardation, attempted suicide, anxiety states, chronic confusion, convulsions, and euphoria (287). In another study it was estimated that 20 per cent of the patients with Cushing's syndrome showed evidence of severe mental disturbances (288).

Parson et al. (334) studied the fecal and urine excretion of N^{15} in Cushing's syndrome and in patients treated with ACTH. They found that in both groups there occurred an increased urinary excretion of N^{15} whether the patients were in nitrogen balance or in negative balance. They suggested that hyperadrenalcorticalism may be characterized by an increased rate of degradation of ingested amino acids and decreased protein synthesis.

An interesting instance of an adrenocortical tumor arising in the liver of a three-year-old boy in whom resection resulted in cure of the mixed Cushing's and virilizing syndrome has been reported (291).

The adrenogenital syndrome.—The work of Wilkins et al. (298 to 301, 339) constitutes a significant contribution to the treatment of congenital adrenal cortical hyperplasia. These workers demonstrated that cortisone is of value not only in reducing the excessive urinary excretion of the neutral 17-ketosteroids and of dehydroisoandrosterone, pregnanediol and pregnantriol (381), and estrogens, but also in decreasing the clinical manifestations of virilism. It is chiefly on the basis of these observations that there has been evolved the cortisone test for differentiating adrenal cortical hyperplasia from adrenal cortical tumor in patients with virilism (316, 317). Following the administration of cortisone the urinary excretion of the neutral 17-ketosteroids falls markedly in the presence of hyperplasia but is reduced slightly if at all in the presence of tumor (316, 317, 335). The clinical manifestations of congenital adrenal cortical hyperplasia are of considerable interest, both from the theoretical and the clinical point of view. There have now been delineated syndromes of androgenic hyperactivity associated with failure of glycogenic corticoid production, with salt wastage, and with hypertension, indicating the dissociation of adrenal function that may be encountered.

When female patients with congenital adrenal cortical hyperplasia are successfully treated, feminization returns and menstruation occurs if the child is at or past the age of puberty. Interestingly enough, puberty occurs at an early age in these children, and apparently the degree of precocity depends upon the developmental rather than the chronological age. Similarly, feminization may be effected in the adult with acquired adrenocortical hyperfunction and virilization.

According to the studies of Wilkins and associates, the initial daily treatment schecule with cortisone should be 50 mg. given intramuscularly for older patients, and 25 mg. intramuscularly in younger patients. This may then be reduced in 5 to 10 days to 25 mg. daily for the former group and 5 to 25 mg. for the younger subjects. The hormone may also be given in a dosage of 75 mg. every third day or 100 mg. every fourth day. When administered orally, the daily amount administered should be two or three times that used intramuscularly. In the older group the beneficial results include development of the breasts, estrogenic vaginal smears, decrease in hirsutism, menstruation and ovulation, and the development of feminine contours. In infants, abnormal growth and osseous development ceases. In boys, growth of the testes occurs. It is of interest to note that during intercurrent stress, such as an infection, the urinary excretion of the neutral 17-ketosteroids rises even while the patient is on cortisone.

Kelley et al. (315) have reported low levels of the 17-hydrocorticoids in the blood of patients with congenital adrenocortical hyperplasia. They also find that the blood levels of ACTH are increased, suggesting that cortisone acts by raising the blood levels of the 17-hydroxycorticoids and thereby inhibiting ACTH production. Jailer has suggested that the virilizing manifestations of this disease may be due to a failure of conversion of 17-hydroxy-progesterone by the adrenal into 17-hydroxycorticoids and that the former fraction is directed into androgen production (214).

Gardner & Migeon (296) have pointed out that in the virilizing syndrome due to tumor the urinary excretion of the neutral 17-ketosteroids, dehydro-isoandrosterone, and estrogens is increased and is unaffected by cortisone. In adrenal hyperplasia with virilism the urinary excretion of the neutral 17-ketosteroids and estrogens is increased, and there may be slight increase in dehydroisoandrosterone excretion. These values return towards normal levels following the administration of cortisone. It is interesting that two instances of benign adrenocortical tumor in males associated with gynecomastia reported by Dohan excreted normal mounts of urinary neutral 17-ketosteroids but large amounts of estrogen (319).

Allen et al. (309) have devised a color test for dehydroisoandrosterone in the urine to facilitate the diagnosis of malignant adrenal cortical tumor. The test is similar to that described by Patterson (310). However, attention must be called to the recent claims that the urinary excretion of dehydroiso-androsterone may be higher in both normal subjects and patients with adrenal cortical hyperplasia than had previously been thought possible (311).

Several interesting reports of androgenic tumors have been published. It is important to note that, in some, hirsutism may be the sole manifestation of a virilizing tumor (312). A feminizing adrenocortical carcinoma associated with prostatic carcinoma has been reported by Myrke (308). This patient had gynecomastia and diminished libido and impotence, and the urinary excretion of the neutral 17-ketosteroids was over 200 mg. per 24 hr. Dohan

and associates (319) reported another instance of a benign adrenal cortical tumor associated with gynecomastia, testicular atrophy, hypertension, and a high urinary estrogen but normal 17-ketosteroid excretion. Carter and Shorr (314) attempted to measure endogenous androgen production by titration against the effects of estrogen. In a classical instance of virilism due to adrenocortical hyperplasia they found that the equivalent of 1500 to 2500 mg. of testosterone was produced per day. It was estimated that to induce vaginal smear changes a dosage of estrogen 133 times that sufficient to induce such changes in the menopausal subject was required.

Congenital adrenal cortical hyperplasia is not infrequently familial, 100 instances occurring in 43 families being reported in the literature (302). The majority of the patients were female pseudohermaphrodites. In this series there was a surprisingly high incidence of Addison's disease, this occurring in 29 patients. Thirty-three of the 100 patients died before the age of six months, and 10 more subsequently succumbed during childhood.

The adrenal medulla: epinephrine and norepinephrine (Arterenol) (392).— Goldenberg (393) has recently reviewed adrenal medullary function. He traced the history of the discovery of norepinephrine, its identification in the adrenal medulla, and its release by sympathetic nerve fibers. The content of medullary norepinephrine in the catecholamine fraction differs in various species, there being little if any present in the rabbit adrenal, approximately 20 per cent in cattle and human adrenals, and about 50 per cent in the cat adrenal. The embryonic glands of mammals show a high proportion of norepinephrine (397). The physiologic form of norepinephrine is the levo compound. Epinephrine causes an increase in cardiac output and pulse rate and a decrease in peripheral resistance, an increase in oxygen consumption, hyperglycemia, adrenal cortical and central nervous system stimulation, and increased cerebral blood flow. Norepinephrine does none of these, or does them to a minor degree, however, it does increase the peripheral resistance markedly. Such an effect of norepinephrine on the peripheral resistance has been employed in the treatment of various forms of shock (406). The effects of these compounds on the circulation has been reviewed by Swan (406) and by von Euler (169).

Pheochromocytoma.—From an analysis of adrenal medullary tumors, Goldenberg (393) has concluded that small pheochromocytomas containing predominantly norepinephrine produce a syndrome mimicking essential hypertension. In patients with tumors containing larger amounts of this fraction, some evidences of hypermetabolism and hyperglycemia were observed. When the predominating amine was epinephrine, hypertension, hypermetabolism (403), hyperglycemia, and tachycardia occurred. However, patients with these latter tumors may present only hypertension as the sole clinical manifestation of the underlying disease and may exhibit a negative benzodioxane response. He points out that hypertension may persist even if the tumor is removed, and suggests that this may be a "secondary hypertension" or possibly a reflection of induced hypercorticism (411). Such

secondary hypertension independent of circulating pressor amines from the medulla is offered as an explanation for the repeated instances in which a negative benzodioxane response is encountered.

Graham (395) has reviewed 207 cases of pheochromocytoma. They were almost equally divided as to sex incidence and the age groups varied from 5 months to 72 years, most occurring in the fifth decade. The tumor was located in the right adrenal in 92 instances, in the left adrenal in 70, in the right lumbar paravertebral space in 7, in the left lumbar paravertebral space in 5; 4 were found in front of great vessels of the abdomen, 4 in the organ of Zuckerkandl, 2 in the left thoracic paravertebral space, and one in the celiac ganglion. Bilateral adrenal tumors (401, 402, 404) were present in 19 patients; three had two extraadrenal tumors (399), one had an adrenal tumor and an extraadrenal neoplasm. Also, 141 patients had paroxysmal hypertension, 21 patients had no hypertension, 30 patients had a constantly elevated blood pressure, and in 98 instances the hypertension was intermittent. Ten per cent of the patients were diabetic and 14 per cent had a palpable tumor. In 100 cases the most common symptoms were headache (55 per cent), palpitation (38 per cent), vomiting (28 per cent), sweating (23 per cent), and dyspnea (19 per cent). The history of duration of symptoms was as great as 32 years. The interval between attacks varied from a few minutes to many months, and the attacks lasted seconds to days. The attacks were particularly prone to occur after a period of quiescence or following pressure on the tumor. The tumor was malignant in 24 instances. In 72 untreated cases the principal causes of death were cerebrovascular accidents and cardiac failure. The average postoperative mortality was 26 per cent prior to the use of adrenergic blocking agents. Glushien *et al.* (412) believe that pheochromocytomas are related to the neurocutaneous syndromes (neurofibromatosis, von Hippel-Lindau disease, Sturge-Weber disease, and tuberous sclerosis). They point out that 10 per cent of the instances of pheochromocytoma are associated with such syndromes, and the presence of neurocutaneous stigmata in association with hypertension warrants investigation for the existence of a possible adrenal medullary tumor. Of particular interest is a report by Cope and associates (411) of a pheochromocytoma found in association with an adrenocortical adenoma. They speculate as to the possible interrelationship in view of the effects of epinephrine on the adrenal cortex.

Pharmacologic tests for pheochromocytoma: blocking agents.—Benzodioxane is effective against both norepinephrine and epinephrine (393). Goldenberg reported 59 proven cases in which positive responses were obtained (393). He suggests that the false negative results reported in proven cases may be due to the nonhumoral phase of hypertension. At least eight such results have been recorded, and false positive results may occur in uremia (332, 393).

Regitine, introduced by Emlet and his group (167) for the diagnosis of pheochromocytoma, was employed by Gifford and associates (398). Follow-

ing the administration of 5 mg. of regitine, a positive response consists of: (a) a drop in the blood pressure exceeding 35 mm. of mercury systolic and 25 mm. diastolic, or a fall to normal levels, and (b) a depressor effect, maximal in 2 min. after intravenous injection of the agent or 20 min. after intramuscular injection. Positive reactions were observed in 3 out of 149 patients with hypertension given the drug intramuscularly and in 4 of 107 patients to whom it was administered intravenously. Although two false negative reactions were observed following intramuscular administration, none was seen in the seven patients with pheochromocytoma given the drug intravenously.

Hypertension inducing agents.—Histamine: Of 16 proven cases of pheochromocytoma, 12 positive and 4 false negative responses were observed (393, 394).

Graham (395), and Shapiro and co-workers (394) have reported on the use of tetraethyl ammonium chloride (TEAC) and methacholine (mecholyl). The former reported one failure with mecholyl in five proven cases of pheochromocytoma, and one failure in four patients when employing TEAC.

The determination of the urinary excretion of norepinephrine and epinephrine as a test for pheochromocytoma has been suggested by Goldenberg (393) and Lund (172). Normal subjects excrete 15 to 45 mg. of norepinephrine, which constitutes approximately 80 per cent of the urinary mixture. In patients with pheochromocytoma, there occurs a very considerable increase in the urinary excretion of this fraction, particularly during paroxysmal hypertensive episodes.

The use of adrenolytic agents has markedly improved the operative outlook (393, 395, 396, 400). The use of benzodioxane or regitine to prevent paroxysmal hypertension during the operative procedure, and the use of norepinephrine postoperatively is now common and well established practice.

THE PARATHYROID GLANDS

Effect of parathyroid hormone.—Further evidence has been advanced to suggest that the action of parathyroid extract (Para-thor-mone) is not entirely on phosphate diuresis. For example, phosphate loss causes osteomalacia but does not produce osteitis fibrosa cystica (413, 414). Indeed, Albright, who has been the staunchest supporter of the action of parathyroid extract on the renal excretion of phosphate, now concedes that this hormone must also exert a direct action on bone (426). Stewart & Bowen (433) maintain that parathyroid extract exerts its effect primarily on bone and that phosphate diuresis is in reality an artefact, particularly since extracts of spleen and thymus prepared similarly to that of parathyroid extract produce a similar renal excretion of phosphorus. Engel (265) found that the administration of parathyroid extract to experimental animals resulted in the solution of the glycoprotein ground substance of bone with a secondary rise in the serum mucoproteins proportional to the dose administered. In addition, renal tubular precipitation of the mucoproteins resulted in tubular

blockage. Klein & Gow (424) studied the effects of parathyroid extract and Vitamin D on the renal excretion of phosphorus in an attempt to explain their effects in rickets and hypoparathyroidism. Parathyroid extract was found to increase the glomerular filtration of phosphate and to reduce its tubular reabsorption. Vitamin D, on the other hand, also increased the glomerular filtration of this ion, but in addition there occurred an increased tubular reabsorption of phosphorus. The latter effect, they believe, results from an inhibition of endogenous parathyroid extract secretion. Vitamin D does not inhibit the action of exogenously administered parathyroid extract.

Howard and co-workers (425) have suggested the use of intravenously administered calcium as a diagnostic test in parathyroid disease. Following such a procedure there normally occurs a rise in serum phosphorus and a fall in urinary phosphorus. In hypoparathyroidism a marked rise in urine phosphorus, but little if any change in serum phosphorus is observed. In hyperparathyroidism little change in either serum or urine phosphorus is noted (425).

Idiopathic hypoparathyroidism.—Steinberg & Waldron (415) reviewed the literature on this disorder. In 52 cases the clinical manifestations included cataracts (52 per cent), poor dentition (36.5 per cent), alterations in the skin, nails, or hair (25 per cent), papilledema (13.5 per cent), fungus infections (13.5 per cent), mental retardation (17 per cent), physical retardation (5.8 per cent), chronic conjunctivitis (3.8 per cent), syndactylism (1.9 per cent), and polydactylism (1.9 per cent). Tetany and convulsions, as well as paresthesias, constipation, vomiting, psychosis, and nervousness occurred in many of the patients (417). Diagnosis is usually established by the presence of chronic tetany associated with a low serum calcium, and a high serum phosphorus level in the absence of renal insufficiency. osteomalacia, and rickets. They suggest the use of dihydrotachysterol (A.T.10) as the treatment of choice.

Postoperative hypoparathyroidism and tetany.—Wijnbladh (420) studied 40 instances of postthyroidectomy tetany. He emphasizes the fact that the diagnosis may be difficult to establish in the absence of overt clinical tetany. Certain stressing situations, including infection or the onset of menses may provoke overt tetany (423). Subjective paresthesias are an important symptom, and ocular cataracts occurred as early as seven months after operation. In his experience, Vitamin D_2 (calciferol) was found to be the drug of choice because of its low cost and its failure to depress endogenous parathyroid activity. However, the dangers of renal impairment resulting from Vitamin D intoxication must be borne in mind. Fortunately, this type of renal insufficiency is usually reversible. Blohm *et al.* (423) reported an instance of postthyroidectomy hypoparathyroidism refractory to A.T.10 and Vitamin D therapy, although the patient did respond to parathormone. An interesting and unique, example of temporary hypoparathyroidism following treatment of hyperthyroidism with I_{131} has been reported (421). Freedberg

et al. (422) studied the histology of the parathyroid bodies in nine euthyroid patients treated with large doses of I_{131} (17 to 157 mc.). In only one instance was there any evidence of abnormality, which consisted of swelling and vacuolization of the oxyphil cells (422).

Hyperparathyroidism. (245)—Woolner and co-workers (427) reviewed pathologic findings in 140 cases of primary hyperparathyroidism seen at the Mayo Clinic. 115 instances were due to single adenomas, in 11 the tumors were multiple, and in two patients the tumors were carcinomatous; there were 12 cases of primary water clear cell hyperplasia. The chief cell adenoma was the commonest type of tumor, but transitional water clear cell or oxyphil cell tumors were also found. One-third of the tumors were of mixed cell types. Included in the group were multiple parathyroid tumors associated with other endocrine tumors of the adenohypophysis or the pancreatic islets. The authors point out that the parathyroid carcinoma may appear benign in spite of invasive tendencies and may resemble a chief cell adenoma. Murphy *et al.* (428) reviewed 25 instances of primary hyperparathyroidism. Twenty-four were due to adenoma and one to diffuse parathyroid hyperplasia. Four of the patients required more than one operation before the parathyroid tumor was found. The importance of the treatment of postoperative tetany is emphasized, particularly in patients with a considerable preoperative elevation of the serum calcium or alkaline phosphatase levels. Schmith & Faber (419) briefly reviewed the subject of primary hyperparathyroidism, illustrating it with four personally observed cases. Emphasis was placed on the renal picture encountered in the disease in the absence of nephrolithiasis or nephrocalcinosis (430). Albright *et al.* (432) recently studied a group of patients with idiopathic hypercalcuria with normal serum calcium levels. These patients usually presented a past or present history of staphylococcal pyelonephritis.

THE THYROID GLAND

The thyroid stimulating hormone.—An anterior pituitary fraction containing thyrotropic and gonadotropic activity was coupled with S_{35}-labeled diazobenzene sulfonic acid. Following administration to the chick this preparation was localized in the thyroid, liver, and gonads (360). An increase in the elaboration of thyrotropin following thyroidectomy was demonstrated by parabiotically uniting hypophysectomized and thyroidectomized rats (376). Tala has reported on a histoquantitative method for the assay of TSH (305).

Parahydroxypropiophenone, which had been claimed to be an inhibitor of thyrotropin (372) was reported to be without effect in Graves' disease (269), and indeed some experimental evidence suggests that it may exercise a goitrogenic effect (366).

Thyroid hormone.—Attention has recently been focused on the physiological activity of 3,5,3-l-triiodotyrosine. It is reported to be three to five times as effective as l-thyroxin, it exerts its maximum effect on oxygen consump-

tion within 8 to 24 hr., and the basal metabolic rate returns to the control levels in eight days as compared to comparable figures of 3 to 10 days and 70 to 80 days for l-thyroxine (282, 283, 284, 330, 373). However, valid basis for comparison of their action is still lacking. It has been suggested that both l-thyroxin and l-triiodotyrosine exercise substantially the same total calorigenic effect (373).

Lerman and co-workers (362) studied several analogues of thyroxin and found that they depress pituitary and thyroid activity only in proportion to their calorigenic effect. Thryoxin activity was markedly decreased by changing the position of the iodine or substitution of other halogens. Alterations in the side chain, substitution of sulfur in the other linkage, and substitution of a methyl group in the hydroxy position exerted little effect (362). Perlmutter and associates attempted to study the mechanism of inhibition of the activity of the thyroid gland following the ingestion of thyroid substance and concluded that the effect is exerted chiefly as a result of adenohypophyseal inhibition (408). Confirmatory evidence for the existence of this regulatory mechanism in euthyroid individuals is afforded by the observation that the serum protein bound iodine level remains constant despite the daily administration of as much as three grains of desiccated thyroid extract. Larger amounts do increase the protein-bound iodine values (246).

In patients given tracer doses of I_{131}, 90 per cent of the serum I_{131} was found to be precipitable with Somogyi reagent and 70 to 80 per cent extractable with n-butanol. Following large therapeutic doses of I_{131} the serum radioactive iodine was largely precipitable but only 12 to 66 per cent was butanol soluble. The butanol insoluble material, following alkaline hydrolysis, yielded diiodotyrosine, thyroxin, and iodide, suggesting the composition of thyroglobulin (313).

In immature rats radioactive l-thyroxin was distributed immediately in the blood (38 per cent), liver (30 per cent), and remaining tissues (32 per cent). Rapid diffusion occurred into the gastrointestinal tract, in part through the bile, and recirculation from the bowel took place through portal and lymphatic drainage. Ultimately one-third of the total radioactivity was observed to be present in the feces and one-third in the urine. Large quantities of radioactive l-thyroxin are secreted into the stomach but are absorbed only from the small and large intestines (431). When radiothyroxine is injected into patients with hyperthyroidism the main metabolic fate of the hormone is deiodination. Part of the iodine is reaccumulated in the thyroid, and part is excreted in the urine (367).

Thyroid glands implanted in the spleen continue to remain normal in structure, and growth of the animal is maintained, The administration of thiouracil results in the usual hyperplastic changes in the gland. These observations would suggest that the liver is not essential for the activation of the thyroid hormone (410). The placenta in the guinea pig was found to be impermeable to TSH but does permit the passage of thiouracil and thyroxine (331). In the rat, cold induces thyroid hyperplasia in association with a nor-

mal protein-bound iodine, indicating an increased peripheral utilization of the thyroid hormone (416). It is interesting to note that the protein-bound iodine and the basal metabolic rate of soldiers stationed in Northern Canada remained unchanged prior and subsequent to their sojourn. However, the protein-bound iodine of Eskimos studied in Massachusetts was slightly higher than that of the native population of that state (268).

Thyroid extract decreased the plasma cholesterol level of cholesterol-fed rats (378). Rosenman and co-workers (361) suggest that the hyperthyroid state is associated with a markedly increased rate of hepatic synthesis, destruction, and intestinal excretion of cholesterol. They suggest that the inverse thyroid activity/blood cholesterol relationship is dependent on this interplay. They also suggest a possible role of bile acid (cholate) metabolism in this cycle.

A thyroxine deficiency syndrome can be produced by feeding thyroidectomized young rats a diet low in iodine and tyrosine. These animals survived at high temperature levels (27°C.) but failed to survive at reduced temperatures (16°C.) (409). Myxedema was produced in the dog with I_{131} (429).

Thyroidectomy decreases the survival rate of irradiated rats. Following the administration of thiourea to castrated mice, there occurs some adrenal cortical hyperplasia rather than the expected adrenal atrophy (379, 385).

Endocrine-thyroidal interrelationship.—In the male guinea pig, the sex drive is not altered either by thyroidectomy or following the administration of thyroxine. The former did cause a slight decrease in fertility. In the female, thyroidectomy decreased the frequency of cyclic vaginal openings, the percentage of animals in heat, of fertile matings, and of young born alive. Propylthiouracil was without effect in these regards (405, 407). Goldsmith *et al.* studied the menstrual pattern of premenopausal women with thyroid disease (273). Oligomenorrhea or amenorrhea occurred in 16 of 17 patients with thyrotoxicosis. In three patients amenorrhea with ovulatory failure and hypoestrinism was found, and in the remaining patients ovulation occurred. In two instances bleeding from a proliferative endometrium was encountered. Normal menstrual patterns recurred following definitive therapy. Seven of ten patients with myxedema showed ovulatory failure presumably due to the inadequate production of luteinizing hormone. Two patients had normal menses with ovulation. One had evidence of an inadequate corpus luteum effect on the endometrium. All resumed a normal pattern on thyroid medication. The thyroid hormone is apparently not essential for the effect of progesterone on basal temperature (326).

Colloid goiter.—A very interesting study of the iodine deficient thyroid gland found in the goitrous regions of the Andes in Mendoza, Argentina, was carried out by Stanbury *et al.* (350). They found that the glands exhibited a marked avidity for iodine, as evidenced by the fact that an uptake of over 60 per cent in 48 hr. was often encountered. Despite a rapid turnover of I_{131} in the gland, the thyroids were apparently not under maximal stimulation

from endogenous thyrotropin since exogenous thyrotropin increased the rate of iodine release. Although dietary supplements of iodine$_{127}$ were ineffective in reducing the I_{131} uptake, the exogenous administration of thyroid extract was found to be quite effective. Money and associates (368) studied the effects of an iodine-deficient diet in the rat. An increase in the thyroidal collection of I_{131} was associated with a decrease in the level of thyroid iodine and in the serum inorganic iodine. A fall in the protein-bound iodine in the serum was quite well correlated with an increase in thyroid size. The effects of the diet could be reversed by the administration of potassium iodide. An interesting instance of goiter in humans resulting from habitual ingestion of rutabaga, cabbage, and turnips has been reported (*Stuma cibaria*) (337). Brush & Altland (364) report a marked reduction in the incidence of endemic goiter in Michigan by the use of iodized salt. They noted a concomitant decrease in toxic nodular and diffuse goiter which they claim are less apt to occur if the previous enlargement of the gland is prevented.

Tests of thyroid function.—Debate still continues over the relative merits of the various tests of thyroid function. Proponents of the use of radioactive iodine differ as to the most effective way of utilizing this tool as a test of thyroid function. The most satisfactory methods for using I_{131} would appear to be the measurement of the uptake of the radioactive moiety by the thyroid (328, 340) and the conversion of I_{131} into the serum protein bound fraction (303, 377).

Hyperthyroidism.—Werner *et al.* (369) have attempted to resolve the question of whether Graves' disease has its primary origin in the thyroid or pituitary gland. It is their belief that hyperthyroidism arises from mechanisms not mediated through the adenohypophysis. Hyperthyroidism may be treated surgically, by the administration of I_{131} (294), or with the use of goitrogens (306, 321). By and large the high incidence of relapse following the use of the various goitrogens, in addition to the necessity for constant and prolonged observation, has caused most clinicians to abandon this mode of therapy. The goitrogens are, however, extremely effective in the preoperative preparation of the patient. The excellent results obtained with I_{131} has resulted in its widespread use in the treatment of hyperthyroidism. However, the possibility of a hypothetical latent carcinogenic effect in humans has caused many physicians to limit its use to patients over the age of 45. In this latter regard, it is important to note the observations of Maloof and co-workers (380) and of Goldberg & Chaikoff (327). The former investigators observed persistent increases in cell height and bizarre nuclear changes in the thyroid of rats followed for as long as 18 months after the administration of 1 to 300 μc. of I_{131}. These observers reported the occurrence of thyroid carcinoma in 7 of 25 rats, one and one-half to two years after the intraperitoneal injection of 400 μc. of I_{131}. Many clinics prefer the use of surgery to I_{131} in the treatment of toxic nodular goiter. Werner *et al.* have emphasized that therapeutic effects may follow the repeated use of tracers of I_{131}, particularly

in children (363). Freedberg and associates (349) maintain that the predictability of the delivered thyroid radiation of a therapeutic dose of I_{131} on the basis of the uptake and biologic half-life following a tracer dose is sufficiently accurate to permit calculated I_{131} dosage. However, their report would suggest that they had not as yet attained this objective.

I_{131}.—Seed & Jaffe (325) have reported their results in 257 patients with hyperthyroidism treated with I_{131} and have compared them with 1720 cases collected from the literature. By and large, in the latter group a satisfactory remission was obtained in 80 per cent, hypothyroidism occurred in 9 per cent, and in 11 per cent the results were incomplete or unsatisfactory. No accurate estimate of the recurrence rate could be given, although there were some suggestions that it probably varied from 3 to 10 per cent. The required dosage of I_{131} in the treatment of hyperthyroidism could not be adequately estimated beforehand. The effect of radioactive iodine on exophthalmos was approximately identical with that produced by thyroidectomy (325). Seed & Jaffe maintained that they have obtained satisfactory results in the treatment of malignant exophthalmos by subjecting the patients to total thyroidectomy, or total destruction of the thyroid with I_{131} and then employing thyroid extract to control the myxedema. In a study of 384 cases of hyperthyroidism treated with radioactive iodine, followed by Clark *et al.* (289) for six months to five years, a satisfactory remission was obtained in 85.2 per cent, and 13.8 per cent developed various degrees of hypothyroidism, while 1 per cent were left with permanent myxedema. No recurrences were observed. Twice as much I_{131} was necessary to induce a remission in patients with toxic nodular goiter as in cases of diffuse hyperplasia. In 76 per cent of the total group, the administration of one or two doses of radioactive iodine was adequate; in the remainder as many as seven doses were necessary. No instance of malignant exophthalmos developed as a result of the treatment (289).

The goitrogens.—Schultz & Jacobson (320), employing I_{131} in human subjects, found supportive evidence that propylthiouracil acts primarily to block hormone synthesis by the thyroid gland. Various anions, such as perchlorate, chlorate, hypochlorite, periodate, iodate, biiodate, and nitrate, share with thiocyanate the properties of inhibiting the collection and the retention of iodide by the thyroid of animals pretreated with propylthiouracil (375).

The more recently clinically employed goitrogens include tapazole (1-methyl-2-mercapto-imidazole), 2-mercapto-imidazole, 6-methyl-2-thiouracil, 6-*n*-propylthiouracil, 5-iodo-2-thiouracil (Itrumil), and 2-thiouracil. According to McGavack, this order represents the decreasing effectiveness of these compounds (290). In a study of 187 cases of hyperthyroidism treated with thiouracil observed from one to seven years, a complete remission was obtained in 130 patients and incomplete remission in 35 more. Fifty-eight patients suffered relapses. In some, the relapse occurred after two to three years of excellent health (338). Stirrett and co-workers (270) reported

on 70 patients treated with methylthiouracil. Their findings confirmed those of others in that they noted initial excellent control of the disease, a fairly high toxicity rate (10 per cent), and a high relapse rate after cessation of therapy (270). Methimazole (Tapazole) was found to be an effective antithyroid agent (261, 293), but because of its toxicity its usefulness is to a considerable extent limited to preoperative preparation of the patient (241, 307). Following treatment with I_{131} the subsequent administration of 1-methyl-2 mercapto imidazole results in an early fall in the protein-bound iodine of the serum. This does not occur following the administration of sodium iodide of 6-propylthiouracil (324). Duffy & Howland emphasize the usefulness of methimazole in inducing a rebound increase in the uptake of I_{131} for the treatment of euthyroid patients with cardiac disease (211).

Catz & Starr (177) noted that the height of the thyroid epithelium of hyperthyroid patients prepared for surgery with iodothiouracil was lower than those prepared by the combined use of Lugol's solution plus thiouracil, propylthiouracil, or methylthiouracil. Finally, the postsurgical incidence of recurrent hyperthyroidism or of postoperative myxedema has not been altered by the preliminary use of goitrogens (333, 365) in the preoperative management of patients with hyperthyroidism.

Hypothyroidism.—Robertson & Kirkpatrick (318) treated patients with hypothyroidism with l-thyroxin and with desiccated thyroid extract and found both agents equally satisfactory. They noted a rise in the protein-bound iodine level of the serum and of 7 per cent in the basal metabolic rate per 0.1 mg. dose of l-thyroxin. They found the basal metabolic rate to be a more satisfactory indicator of proper dosage than the protein-bound iodine level of the serum and that daily dosages as high as five grains of thyroid extract or 0.5 mg. thyroxin were necessary in some instances to maintain the patients in a euthyroid state.

Thyroiditis.—Lindsay and co-workers (374) reported a clinicopathologic study of 354 patients with chronic thyroiditis. They found a significantly higher incidence of malignant thyroid neoplasm in association with Hashimoto's disease than in glands free of inflammatory disease.

LITERATURE CITED

1. Purves, H. D., and Griesbach, W. E., *Endocrinology*, **49**, 244 (1951)
2. Purves, H. D., and Griesbach, W. E., *Endocrinology*, **49**, 427 (1951)
3. Purves, H. D., and Griesbach, W. E., *Endocrinology*, **49**, 652 (1951)
4. Halmi, N. S., *Endocrinology*, **47**, 289 (1950)
5. Halmi, N. S., *Endocrinology*, **50**, 140 (1952)
6. Golden, A., Bondy, P. K., and Sheldon, W. H., *Proc. Soc. Exptl. Biol. Med.*, **74**, 455 (1950)
7. Laqueur, G. L., *Science*, **112**, 429 (1950)
8. Golden, A., and Bondy, P. K., *Proc. Soc. Exptl. Biol. Med.*, **79**, 252 (1952)
9. Whittlestone, W. G., *J. Endocrinol.*, **8**, 89 (1952)
10. Li, C. H., *Harvey Lectures*, *Ser. 46*, 181 (1952)
11. Wilhelmi, A. E., Fishman, J. B., and Russell, J. A., *J. Biol. Chem.*, **176**, 735 (1948)
12. Geschwind, I. I., and Li, C. H., *J. Clin. Endocrinol. and Metabolism* (Abstr.), **12**, 937 (1952)
13. Sonenberg, M., Money, W. L., Rawson, R. W., and Keston, A. S., *J. Clin. Endocrinol. and Metabolism* (Abstr.), **12**, 938 (1952)
14. Cross, B. A., and Harris, G. W., *J. Endocrinol.*, **8**, 148 (1952)
15. Whitney, J. E., Bennett, L. L., and Li, C. H., *Proc. Soc. Exptl. Biol. Med.*, **79**, 584 (1952)
16. Glafkides, C. M., and Bennett, L. L., *Proc. Soc. Exptl. Biol. Med.*, **77**, 524 (1951)
17. Batts, A. A., and Bennett, L. L., *J. Clin. Endocrinol.*, **11**, 753 (1951)
18. Russell, J. A., *Endocrinology*, **49**, 99 (1951)
19. Ulrich, F., Reinhardt, W. O., and Li, C. H., *Endocrinology*, **49**, 213 (1951)
20. Scow, R. O., *Endocrinology*, **49**, 641 (1951)
21. Selye, H., *Endocrinology*, **49**, 197 (1951)
22. Selye, H., *Acta Endocrinol.*, **9**, 337 (1952)
23. Berlin, N. I., Van Dyke, D. C., Siri, W. E., and Williams, C. P., *Endocrinology*, **47**, 429 (1950)
24. Van Dyke, D. C., Simpson, M. E., Garcia, J. F., and Evans, H. M., *Proc. Soc. Exptl. Biol. Med.*, **81**, 574 (1952)
25. Gaebler, O. H., and Mathies, J. C., *Endocrinology*, **48**, 623 (1951)
26. Young, F. G., *J. Clin. Endocrinol.*, **11**, 531 (1951)
27. Engel, F. L., *Endocrinology*, **50**, 100 (1952)
28. de Bodo, R. C., Kurtz, M., Ancowitz, A., and Kiang, S. P., *Am. J. Physiol.*, **163**, 310 (1950)
29. Russell, J. A., *Endocrinology*, **48**, 462 (1951)
30. Lukens, F. D. W., *Proc. Am. Diabetes Assoc.*, **10**, 103 (1950)
31. Long, C. N. H., and Lukens, F. D. W., *J. Exptl. Med.*, **63**, 465 (1936)
32. Long, C. N. H., Katzin, B., and Fry, E., *Endocrinology*, **26**, 309 (1940)
33. Young, F. G., *Biochem. J. (London)*, **39**, 515 (1945)
34. de Bodo, R. C., Kurtz, M., Ancowitz, A., and Kiang, S. P., *Federation Proc.*, **9**, 30 (1950)
35. de Bodo, R. C., Kurtz, M., Ancowitz, A., and Kiang, S. P., *Proc. Soc. Exptl. Biol. Med.*, **74**, 524 (1950)
36. de Bodo, R. C., Sinkoff, M. W., Kiang, S. P., and Den, H., *Proc. Soc. Exptl. Biol. Med.*, **81**, 425 (1952)
37. Campbell, J., Lei, H. P., and Davidson, I. W. F., *Endocrinology*, **49**, 635 (1951)

38. Campbell, J., Davidson, I. W. F., Snair, W. D., and Lei, H. P., *Endocrinology,* **46,** 273 (1950)
39. Kurtz, M., de Bodo, R. C., Kiang, S. P., and Ancowitz, A., *Proc. Soc. Exptl. Biol. Med.,* **76,** 21 (1951)
40. Milman, A. E., and Russell, J. A., *Endocrinology,* **47,** 114 (1950)
41. de Bodo, R. C., Kurtz, M., Sinkoff, M. W., and Kiang, S. P., *Proc. Soc. Exptl. Biol. Med.,* **80,** 345 (1952)
42. de Bodo, R. C., Sinkoff, M. W., and Kiang, S. P., *Proc. Soc. Exptl. Biol. Med.,* **80,** 350 (1952)
43. Carballeira, A., Elrick, H., MacKenzie, K. R., and Browne, J. S. L., *Proc. Soc. Exptl. Biol. Med.,* **81,** 15 (1952)
44. Bennett, L. L., Weinberger, H., Escamilla, R., Margen, S., and Li, C. H., *J. Clin. Endocrinol.,* **10,** 492 (1950)
45. Lewis, R. A., Klein, R., and Wilkins, L., *J. Clin. Invest.,* **29,** 460 (1950)
46. Shorr, E., Carter, A. C., Kennedy, B. J., and Smith, R. W., Jr., *J. Clin. Endocrinol. and Metabolism* (Abst.), **13,** 865 (1953)
47. Raben, M. S., and Westermeyer, V. W., *Proc. Soc. Exptl. Biol. Med.,* **78,** 550 (1951)
48. Raben, M. S., and Westermeyer, V. W., *Proc. Soc. Exptl. Biol. Med.,* **80,** 83 (1952)
49. Raben, M. S., Westermeyer, V. W., and Leaf, A., *J. Clin. Invest.,* **31,** 655(1952)
50. Kinsell, L. W., Margen, S., Partridge, J. W., Michaels, G. D., Balch, H. E., and Jahn, J., *J. Clin. Endocrinol. and Metabolism,* **13,** 861 (1953)
51. Hsieh, K. M., Wang, T.-Y., and Blumenthal, T., *Endocrinology,* **51,** 298 (1952)
52. Kriss, J. P., and Futcher, P. H., *J. Clin. Endocrinol.,* **8,** 380 (1948)
53. Reid, E., *J. Endocrinol.,* **8,** 50 (1952)
54. Reid, E., *Ciba Colloqium on Endocrine Interrelationships in Carbohydrate Metabolism* (Blakiston & Co., New York, N. Y., 1952)
55. Condiffe, P. G., and Li, C. H., *Federation Proc.,* **11,** 198 (1952)
56. LeMonde, P., Panisset, N., Dobija, M., and Selye, H., *J. Clin. Endocrinol. and Metabolism,* **12,** 973 (1952)
57. Stein, B., *Am. J. Physiol.,* **171,** 587 (1952)
58. Young, F. G., *Brit. Med. J.,* **II,** 1167 (1951)
59. Barns, H. H. F., and Swyer, G. I. M., *Brit. Med. J.,* **II,** 915 (1952)
60. Reid, E., *Nature,* **168,** 878 (1951)
61. Black, K. O., MacDougall, I., Reid, E., and Young, F. G., *Lancet,* **I,** 19 (1952)
62. Long, C. N. H., *Lancet,* **I,** 325 (1952)
63. Ershoff, B., *Endocrinology,* **48,** 111 (1951)
64. Smith, M. C., Slattery, P. A., Shimkin, M. B., Li, C. H., Lee, R., Clarke, J. C., and Lyons, W. R., *Cancer Research,* **12,** 59 (1952)
65. Bartlett, P. D., and Glynn, M., *J. Biol. Chem.,* **187,** 253 (1950)
66. Sprinson, D., and Rittenberg, D., *J. Biol. Chem.,* **180,** 707 (1949)
67. Milman, A. E., DeMoor, P., and Lukens, F. D. W., *Am. J. Physiol.,* **166,** 354 (1951)
68. Bigland, B., and Jehring, B., *J. Physiol.* (*London*), **116,** 129 (1952)
69. Illingworth, B. A., and Russell, J. A., *Endocrinology,* **48,** 423 (1951)
70. de Bodo, R. C., Schwartz, I. L., Greenberg, J., Kurtz, M., Earle, D. P., Jr., and Farber, S. J., *Proc. Soc. Exptl. Biol. Med.,* **76,** 608 (1951)
71. Reinhardt, W. O., and Li, C. H., *Am. J. Physiol.,* **167,** 820 (1951)

72. Leaf, A., Rasmussen, H., Mamby, A. R., and Raben, M. S., *J. Clin. Invest.*, **31**, 646 (1952)
73. Kellgren, J. H., Ball, J., and Tutton, G. K., *Quart. J. Med.*, **21**, 405 (1952)
74. Williams, R. H., and Hogness, J. R., *J. Clin. Endocrinol. and Metabolism*, **12**, 943 (1952)
75. Ormos, J., and Monus, B. Z., *Schweiz. Z. allgem. Pathol. u. Bakteriol.*, **15**, 29 (1952)
76. Underdahl, L. O., Woolner, L. B., and Black, B. M., *J. Clin. Endocrinol. and Metabolism*, **13**, 20 (1952)
77. Iversen, K., *Acta Med. Scand.*, **142**, 1 (1952)
78. Villaverde, M. M., *J. Clin. Endocrinol. and Metabolism*, **12**, 966 (1952)
79. McCullagh, E. P., Beck, J. C., and Schaffenburg, C. A., *Cleveland Clinic Quart.*, **19**, 121 (1952)
80. Thompson, W. O., Thompson, W. K., and Mandernach, D. M., *J. Clin. Endocrinol. and Metabolism*, **12**, 943 (1952)
81. Forbes, A. P., Henneman, P. H., Griswold, G. C., and Albright, F., *J. Clin. Endocrinol.* (Abstr.), **11**, 749 (1951)
82. Argonz, J., and del Castillo, E. B., *J. Clin. Endocrinol. and Metabolism*, **13**, 79 (1953)
83. Ahumada, J. C., and del Castillo, E. B., *Bol. Soc. obstet. y ginecol. Buenos Aires*, **11**, 64 (1932)
84. Sheehan, H. L., and Summers, O. K., *Quart. J. Med.*, **18**, 319 (1949)
85. Perkins, R. F., and Rynearson, E. A., *J. Clin. Endocrinol. and Metabolism*, **12**, 574 (1952)
86. Gabrilove, J. L., and Dorrance, W. R., *Med. Clin. N. Amer.*, 739 (1952)
87. Escamilla, R. F., and Lisser, H., *J. Clin. Endocrinol.*, **2**, 65 (1942)
88. Farquharson, R. F., *Simmonds' Disease* (Charles C Thomas, Publisher, Springfield, Ill., 93 pp., 1950)
89. Soffer, L. J., and Gabrilove, J. L., *Metabolism*, **1**, 236 (1952)
90. Paschkis, K. E., and Cantarow, A., *Ann. Internal Med.*, **34**, 669 (1951)
91. Querido, A., and Stanley, J. B., *J. Clin. Endocrinol.*, **10**, 1192 (1950)
92. Hubble, D., *Lancet*, **I**, 1123 (1952)
93. Howard, R. P., Sniffen, R. C., Simmons, F. A., and Albright, F., *J. Clin. Endocrinol.*, **10**, 121 (1950)
94. D'Angelo, S. A., Paschkis, K. E., Gordon, A. S., Cantarow, A., *J. Clin. Endocrinol.*, **11**, 1237 (1951)
95. Luft, R., and Olivecrona, H., *J. Neurosurg.*, **10**, 301 (1953)
96. Hewer, T. F., *J. Endocrinol.*, **3**, 397 (1944)
97. Oelbaum, M. H., *Brit. Med. J.*, **II**, 110 (1952)
98. Albright, F., and Elrick, H., *Trans. Assoc. Am. Physicians*, **61**, 42 (1948)
99. Plaut, A., *Am. J. Pathol.*, **28**, 883 (1952)
100. Hertz, H., *Act. Med. Scand.*, Suppl. 266, **142**, 523 (1952)
101. Schneeberg, N. G., Perloff, W. H., and Israel, S. L., *J. Clin. Endocrinol. and Metabolism*, **13**, 884 (1953)
102. Murdoch, R., and Govan, A. D. T., *J. Obstet. Gynecol. Brit. Empire*, **58**, 18 (1951)
103. Summers, V. K., *Brit. Med. J.*, **I**, 787 (1952)
104. Crafts, C., *Anat. Record*, **112**, 322 (1952)
105. Sheehan, H. L., and Summers, V. L., *Brit. Med. J.*, **I**, 1214 (1952)

106. Caughey, J. E., James, A., and MacLeod, E. K., *Brit. Med. J.*, **I**, 1216 (1952)
107. Allott, E. N., and Simmons, J. H., *Brit. Med. J.*, **II**, 569 (1951)
108. Rolland, C. F., and Mathews, J. D., *Brit. Med. J.*, **I**, 1220 (1952)
109. Simpson, S. L., *Brit. Med. J.*, **I**, 724 (1952)
110. Shimkin, M. B., Boldrey, E. B., Kelly, K. H., Bierman, H. R., Ortega, P., and Naffziger, H. C., *J. Clin. Endocrinol. and Metabolism*, **12**, 439 (1952)
111. Thorn, G. W., Jenkins, D., Arons, W. L., and Frawley, T. F., *J. Clin. Endocrinol. and Metabolism*, **13**, 957 (1953)
112. Moon, H. D., Simpson, M. E., and Evans, H. M., *Science*, **116**, 331 (1952)
113. Shuman, C. R., *J. Clin. Endocrinol. and Metabolism*, **13**, 795 (1953)
114. Howard, R. P., Mills, E. S., and Mathews, W. H., *J. Clin. Endocrinol. and Metabolism*, **12**, 974 (1952)
115. Statland, H., and Lerman, J., *J. Clin. Endocrinol.*, **10**, 1401 (1950)
116. Ulrich, F., Reinhardt, W. O., and Li, C. H., *Acta Endocrinol.*, **10**, 117 (1952)
117. Younghusband, O. Z., Horrax, G., Hurxthal, L. M., Hare, H. F., and Poppen, J. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 611 (1952)
118. Horrax, G., Hare, H. F., Poppen, J. L., Hurxthal, L. M., and Younghusband, O. Z., *J. Clin. Endocrinol. and Metabolism*, **12**, 631 (1952)
119. Aitken, H. M., and Pohle, E. A., *Wiscon. Med. J.*, **51**, 666 (1952)
120. Landau, D., and Gordon, A. S., *Endocrinology*, **51**, 157 (1952)
121. Harris, G. W., *Brit. Med. J.*, **II**, 559 (1951)
122. Harris, G. W., *Brit. Med. J.*, **II**, 627 (1951)
123. McDermott, W. V., Fry, E. G., Brobeck, J. R., and Long, C. N. H., *Yale J. Biol. and Med.*, **23**, 52 (1950)
124. Sayers, G., *Physiol. Revs.*, **30**, 241 (1950)
125. Scow, R. O., and Greer, M. A., *J. Clin. Endocrinol. and Metabolism* (Abstr.), **13**, 855 (1953)
126. Slusher, M. A., and Roberts, S., *J. Clin. Endocrinol. and Metabolism* (Abstr.), **13**, 859 (1953)
127. Bauer, H. G., *J. Clin. Endocrinol. and Metabolism* (Abstr.), **13**, 858 (1953)
128. Greer, M. A., *J. Clin. Endocrinol. and Metabolism*, **12**, 1259 (1952)
129. Jensen, J. M., and Clark, D. E., *J. Lab. and Clin. Med.*, **38**, 663 (1951)
130. Cheng, C. P., Sayers, G., Goodman, L. S., and Swinyard, C. A., *Am. J. Physiol.*, **159**, 426 (1949)
131. Tang, P. C., and Patton, H. D., *Endocrinology*, **49**, 86 (1951)
132. Van Dyke, H. B., *Bull. N. Y. Acad. Med.*, **29**, 24 (1953)
133. Heller, H., and Zaimis, E. J., *J. Physiol.* (*London*), **109**, 162 (1949)
134. Lauson, H. D., *Am. J. Med.*, **11**, 135 (1951)
135. Turner, R. A., Pierce, J. G., and Du Vigneaud, V., *J. Biol. Chem.*, **191**, 21 (1951)
136. Baez, S., Mazur, A., and Shorr, E., *Am. J. Physiol.*, **169**, 123 (1952)
137. Barrnett, R. J., and Greep, R. O., *Endocrinology*, **49**, 337 (1951)
138. Perry, W. F., and Fyles, T. W., *J. Clin. Endocrinol. and Metabolism*, **13**, 64 (1953)
139. Bernstein, S. H., Weston, R. E., Ross, G., Grossman, J., Hanenson, I., and Leiter, L., *J. Clin. Invest.*, **32**, 422 (1953)
140. Leaf, A., Mamby, A. R., Rasmussen, H., and Marasco, J. P., *J. Clin. Invest.*, **31**, 914 (1952)
141. Leaf, A., and Mamby, A. R., *J. Clin. Invest.*, **31**, 60 (1952)
142. Leaf, A., and Mamby, A. R., *J. Clin. Invest.*, **31**, 54 (1952)

143. Rieber, C. W., and Silver, S., *Ann. Internal Med.*, **37**, 379 (1952)
144. Spillane, J. D., *Thorax*, **7**, 134 (1952)
145. White, A. G., Rubin, G., and Leiter, L., *J. Clin. Invest.*, **30**, 1287 (1931)
146. Nelson, W. P., III, and Welt, L. G., *J. Clin. Invest.*, **31**, 392 (1952)
147. Birnie, J. H., Eversole, W. J., Boss, W. R., Osborn, C. M., and Gaunt, R., *Endocrinology*, **47**, 1 (1950)
148. Chart, J. J., and Shipley, E. S., *J. Clin. Invest.* (Abstr.), **32**, 560 (1953)
149. Stein, M., Jinks, R., and Mirsky, I. A., *Endocrinology*, **51**, 492 (1952)
150. Heller, H., *J. Endocrinol.*, **8**, 215 (1952)
151. de Bodo, R. C., and Sinkoff, M. W., *Ann. N. Y. Acad. Sci.*, **57**, 23 (1953)
152. Astwood, E. B., Raben, M. S., and Payne, R. W., *Recent Progr. Hormone Research*, **7**, 1 (1952)
153. Dedman, M. L., Farmer, T. H., Morris, P., and Morris, C. J. O. R., *Recent Progr. Hormone Research*, **7**, 59 (1952)
154. Long, C. N. H., *Recent Progr. Hormone Research*, **7**, 75 (1952)
155. Liddle, G. W., Rinfret, A. P., Richard, J., and Forsham, P. H., *J. Clin. Endocrinol. and Metabolism*, **13**, 842 (1953)
156. Sorkin, S. Z., and Soffer, L. J., *Metabolism*, **2**, 404 (1953)
157. Li, C. H., *Acta Endocrinol.*, **10**, 255 (1952)
158. Sayers, G., White, A., and Long, C. N. H., *J. Biol. Chem.*, **149**, 425 (1943)
159. Farrell, G. L., and McCann, S. M., *Endocrinology*, **50**, 274 (1952)
160. Overbeck, G. A., and Der Vries, J. Van, *Acta Endocrinol.*, **9**, 309 (1952)
161. Thing, E., *Acta Endocrinol.*, **10**, 295 (1952)
162. Sulman, F. G., *Acta Endocrinol.*, **10**, 320 (1952)
163. Sulman, F. G., *Acta Endocrinol.*, **11**, 1 (1952)
164. Thing, E., *Acta Endocrinol.*, **11**, 362 (1952)
165. Hechter, O., Zaffaroni, A., Jacobsen, R. P., Levy, H., Jeanloz, R. W., Schenker, V., and Pincus, G., *Recent Progr. Hormone Research*, **6**, 215 (1951)
166. Haines, W. J., *Recent Progr. Hormone Research*, **7**, 255 (1952)
167. Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S., *J. Am. Med. Assoc.*, **146**, 1383 (1951)
168. Sweat, M. L., and Farrell, G. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 968 (1952)
169. von Euler, U. S., *Scand. J. Clin. & Lab. Invest.*, **4**, 254 (1952)
170. Saffran, M., Grad, B., and Bayliss, M. J., *Endocrinology*, **50**, 639 (1952)
171. Hayashada, T., and Li, C. H., *Endocrinology*, **50**, 187 (1952)
172. Lund, A., *Scand. J. Clin. & Lab. Invest.*, **4**, 263 (1952)
173. Simpson, S. A., and Tait, J. F., *Endocrinology*, **50**, 150 (1952)
174. Marcus, F., Romanoff, L., and Pincus, G., *Endocrinology*, **50**, 286 (1952)
175. Tait, J. F., Simpson, S. A., and Grundy, H. M., *Lancet*, **I**, 122 (1952)
176. Grundy, H. M., Simpson, S. A., Tait, J. F., and Woodford, M., *Acta Endocrinol.*, **11**, 199 (1952)
177. Catz, B., and Starr, P., *J. Clin. Endocrinol. and Metabolism*, **12**, 228 (1952)
178. Bacchus, H., and Altszuler, N., *Endocrinology*, **51**, 1 (1952)
179. Nadel, E. M., and Schneider, J. J., *Endocrinology*, **51**, 5 (1952)
180. Bacchus, H., Heiffer, M. H., and Altszuler, N., *Endocrinology*, **51**, 94 (1952)
181. Bacchus, H., Altszuler, N., and Heiffer, M. H., *Endocrinology*, **51**, 302 (1952)
182. Bacchus, H., *Endocrinology*, **51**, 576 (1952)

183. Herrick, E. H., Mead, E. R., Egerton, B. W., and Hughes, J. S., *Endocrinology*, **50**, 259 (1952)
184. Clayton, B. E., and Prunty, F. T. G., *Brit. Med. J.*, **II**, 927 (1951)
185. Winters, R. W., Schultz, R. B., and Krehl, W. A., *Endocrinology*, **50**, 377 (1952)
186. Schultz, R. B., Winters, R. W., and Krehl, W. A., *Endocrinology*, **51**, 336 (1952)
187. Bloodworth, J. M. B., *Endocrinology*, **50**, 174 (1952)
188. Hofmann, F. G., *Endocrinology*, **50**, 206 (1952)
189. Gaudino, M., and Levitt, M. F., *J. Clin. Invest.*, **28**, 1487 (1949)
190. Roberts, K. E., and Pitts, R. F., *Endocrinology*, **50**, 51 (1952)
191. Greep, R. O., Knobil, E., Hofmann, F. G., and Jones, T. L., *Endocrinology*, **50**, 664 (1952)
192. de Bodo, R. C., Schwartz, I. H., Greenberg, J., Kurtz, M., Earle, D. P., Jr., and Farber, S. J., *Proc. Soc. Exptl. Biol. Med.*, **76**, 612 (1951)
193. White, H. L. C., Heinbecker, P., and Rolf, D., *Am. J. Physiol.*, **165**, 442 (1951)
194. Boss, W. R., Osborn, C. M., and Renzi, A. A., *Endocrinology*, **51**, 66 (1952)
195. Friedman, S. M., Friedman, C. L., and Nakashima, M., *Endocrinology*, **51**, 401 (1952)
196. Masson, G. M. C., Corcoran, A. C., and Page, I. H., *J. Clin. Endocrinol.*, **11**, 794 (1951)
197. Hall, C. E., and Hall, O., *Endocrinology*, **50**, 478 (1952)
198. Perera, G. A., and Pines, K. L., *Proc. Soc. Exptl. Biol. Med.*, **71**, 443 (1949)
199. Woodbury, D. M., Rosenberg, C. A., and Sayers, G., *Federation Proc.*, **9**, 139 (1950)
200. Soffer, L. J., Gabrilove, J. L., and Jailer, J. W., *Proc. Soc. Exptl. Biol. Med.*, **71**, 117 (1949)
201. Soffer, L. J., Gabrilove, J. L., and Dorrance, W. R., *Proc. Soc. Exptl. Biol. Med.*, **76**, 763 (1951)
202. Migeon, C. J., Gardner, L. I., Crigler, J. F., Jr., and Wilkins, L., *Endocrinology*, **51**, 117 (1952)
203. Halmi, N. S., and Barker, S. B., *Endocrinology*, **51**, 127 (1952)
204. Halmi, N. S., *Proc. Soc. Exptl. Biol. Med.*, **80**, 175 (1952)
205. Woodbury, D. M., Ghosh, B. N., and Sayers, G., *J. Clin. Endocrinol.*, **11**, 761 (1951)
206. Boatman, J. B., Russ, C., Sunder, J. H., Konnerth, A., and Moses, C., *Endocrinology*, **50**, 134 (1952)
207. Perry, W. F., *Endocrinology*, **49**, 284 (1952)
208. Albert, A., Tenney, A., and Ford, E., *Endocrinology*, **50**, 324 (1952)
209. Padawer, J., and Gordon, A. S., *Endocrinology*, **51**, 52 (1952)
210. Hull, W., and White, A., *Endocrinology*, **51**, 210 (1952)
211. Duffy, B. J., Jr., and Howland, J. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 761 (1952)
212. Nichols, J., and Sheehan, H. L., *Endocrinology*, **51**, 362 (1952)
213. Nelson, A. A., and Woodward, C., *Arch. Pathol.*, **48**, 387 (1949)
214. Jailer, J. W., *Bull. N. Y. Acad. Med.*, **29**, 377 (1953)
215. Schrickes, J. A., Fisher, G. R., Tullner, W. W., and Hertz, R., *Endocrinology*, **51**, 394 (1952)
216. Engel, F. L., *Recent Progr. Hormone Research*, **6**, 277 (1951)
217. Engel, F. L., *Endocrinology*, **50**, 462 (1952)

218. Seligman, A. L., and Ashbel, R., *Endocrinology*, **50**, 338 (1952)
219. Ingle, D. J., *Diabetes*, **1**, 345 (1952)
220. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G., *J. Am. Med. Assoc.*, **137**, 1005 (1948)
221. Recant, L., Hume, D., Forsham, P. H., and Thorn, G. W., *J. Clin. Endocrinol.*, **10**, 187 (1950)
222. Best, W. R., Muehrcke, R. C., and Kark, R. M., *J. Clin. Invest.*, **31**, 733 (1952)
223. Thorn, G. W., Goetz, F. C., Streeten, D. H. P., Dingman, J. F., and Arons, W. L., *J. Clin. Endocrinol. and Metabolism*, **13**, 604 (1953)
224. Thorn, G. W., *J. Clin. Endocrinol. and Metabolism*, **13**, 614 (1953)
225. Drekter, I. J., Heisler, A., Scism, G. R., Stern, S., Pearson, S., and McGavack, T. H., *J. Clin. Endocrinol. and Metabolism*, **12**, 55 (1952)
226. Dingemanse, E., Veld, L. G. H. in't., and Hartogh-Katz, S. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 55 (1952)
227. Hetzel, B. S., Hine, D. C., and Stenhouse, N. S., *J. Clin. Endocrinol. and Metabolism*, **12**, 296 (1952)
228. Booker, W. M., Johnson, J. B., Hayes, R. L., Thomas, R. F., Henry, W., Tureman, J. R., and Dent, F., *J. Clin. Endocrinol. and Metabolism*, **12**, 346 (1352)
229. Berson, S. A., and Yalow, R. S., *J. Clin. Endocrinol. and Metabolism*, **12**, 407 (1952)
230. Frederickson, D. S., Forsham, P. H., and Thorn, G. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 541 (1952)
231. Kuhl, W. J., Jr., and Ziff, M., *J. Clin. Endocrinol. and Metabolism*, **12**, 554 (1952)
232. Rosenberg, C. A., Woodbury, D. M., and Sayers, G., *J. Clin. Endocrinol. and Metabolism*, **12**, 666 (1952)
233. Gordan, E. S., Kelsey, C., and Meyer, E. S., *Proc. Clin. ACTH Conf. 2nd Conf.*, **I**, (1951)
234. Renold, A. E., Jenkins, D., Forsham, P. A., and Thorn, G. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 763 (1952)
235. Sydnor, K. L., and Sayers, G., *J. Clin. Endocrinol. and Metabolism*, **12**, 920 (1952)
236. Bowers, J. Z., Nelson, D. H., Bay, R., and Samuels, L. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 921 (1952)
237. Nelson, D. H., Sandberg, A. A., Palmer, J. G., and Glenn, E. M., *J. Clin. Endocrinol. and Metabolism*, **12**, 936 (1952)
238. Porter, C., and Silber, R. H., *J. Biol. Chem.*, **185**, 201 (1950)
239. Carroll, K. K., McAlpine, H. J., and Noble, R. L., *Canad. Med. Assoc. J.*, **65**, 363 (1951)
240. Krupp, M. A., Engelman, E. P., Welsh, J. E., and Wrenn, H. T., *J. Clin. Endocrinol. and Metabolism*, **12**, 1163 (1952)
241. Stone, H. H., Petit, D. W., and Starr, P., *J. Clin. Endocrinol. and Metabolism*, **12**, 841 (1952)
242. Meyer, R. J., *J. Clin. Endocrinol. and Metabolism*, **13**, 123 (1953)
243. Knowlton, A. I., *Med. Clin. N. Amer.*, **36**, 721 (1952)
244. Masuda, M., and Thuline, H. C., *J. Clin. Endocrinol. and Metabolism*, **13**, 581 (1953)
245. Hoffman, G. T., *Surg. Gynecol. Obstet.* (*Intern. Abstr. Surg.*), **95**, 417 (1952)
246. Danowski, T. S., Huff, S. J., Tarail, R., Wirth, P., Peters, J. H., Mateer, F. M., and Garver, K., *J. Clin. Endocrinol. and Metabolism*, **12**, 1572 (1952)

247. Rubin, B. L., Rosenkrantz, H., Dorfman, R. I., and Pincus, G., *J. Clin. Endocrinol. and Metabolism*, **13**, 568 (1953)
248. Nelson, D. H., Samuels, L. T., Willardson, D. G., and Tyler, F. H., *J. Clin. Endocrinol.*, **11**, 1021 (1951)
249. Sandberg, A. A., Nelson, D. H., Palmer, J. G., Samuels, J. L., and Tyler, F. H., *J. Clin. Endocrinol. and Metabolism*, **13**, 629 (1953)
250. Gemzell, C. A., *Endocrinology*, **50**, 399 (1952)
251. Plate, W. P., *Acta Endocrinol.*, **11**, 119 (1952)
252. Gemzell, C. A., *Acta Endocrinol.*, **11**, 221 (1952)
253. Hamburger, C., *Acta Endocrinol.*, **11**, 283 (1952)
254. Warming-Larsen, A., Hamburger, C., and Sprechler, M., *Acta Endocrinol.*, **11**, 400 (1952)
255. Sjögren, B., *Acta Endocrinol.*, **10**, 40 (1952)
256. Levitt, M. F., and Bader, M. E., *Am. J. Med.*, **11**, 715 (1951)
257. Soffer, L. J., Gabrilove, J. L., and Jacobs, M. D., *J. Clin. Invest.*, **28**, 1091 (1949)
258. Luft, R., and Sjögren, B., *Acta Endocrinol.*, **10**, 49 (1952)
259. Ulrich, F., Reinhardt, W. O., and Li, C. H., *Acta Endocrinol.*, **10**, 97 (1952)
260. Soffer, L. J., Gabrilove, J. L., and Jailer, J. W., *J. Clin. Endocrinol.*, **10**, 594 (1950)
261. Bornstein, J., Gray, C. H., and Parrott, D. M. V., *J. Endocrinol.*, **8**, 40 (1952)
262. Godlowski, Z. Z., *J. Endocrinol.*, **8**, 102 (1952)
263. Kazahan, S., *J. Endocrinol.*, **8**, 211 (1952)
264. Sulman, F. G., *J. Endocrinol.*, **8**, 275 (1952)
265. Engel, M. B., *Arch. Pathol.*, **53**, 339 (1952)
266. Verzar, F., and Vidovič, V., *J. Endocrinol.*, **8**, 321 (1952)
267. Lane, N., and de Bodo, R. C., *Am. J. Physiol.*, **168**, 1 (1952)
268. Gottschalk, C. W., and Riggs, D. S., *J. Clin. Endocrinol. and Metabolism*, **12**, 235 (1952)
269. Brady, R. O., and Hedges, T., *J. Clin. Endocrinol. and Metabolism*, **12**, 604 (1952)
270. Stirrett, R. L., Petit, D. W., and Starr, P., *J. Clin. Endocrinol. and Metabolism*, **12**, 719 (1952)
271. Soffer, L. J., and Gabrilove, J. L., *Metabolism*, **1**, 504 (1952)
272. Oleesky, S., *Lancet*, **I**, 769 (1953)
273. Goldsmith, R. E., Sturgis, S. H., Lerman, J., and Stanbury, J. B., *J. Clin. Endocrinol. and Metabolism*, **12**, 846 (1952)
274. Maloney, P. J., *Arch. Internal Med.*, **90**, 869 (1952)
275. Butterly, J. M., Fishman, L., Seckler, J., and Steinberg, A., *Ann. Internal Med.*, **37**, 930 (1952)
276. Wallach, J. B., and Scharfman, W. B., *J. Am. Med. Assoc.*, **148**, 729 (1952)
277. Crawford, M. D., *J. Pathol. Bact.*, **63**, 365 (1951)
278. Tucker, H. St. G., Jr., Taliaferro, I., Kirkland, R. H., and Irby, R., *Am. J. Med. Sci.*, **223**, 479 (1952)
279. Schwartz, H., Derrick, W. S., and Papper, E. M., *Surg. Gynecol. Obstet.*, **94**, 455 (1952)
280. Gaunt, R., Leathem, J. H., Howell, C., and Antonchak, N., *Endocrinology*, **50**, 521 (1952)
281. Groen, J., Pelser, H., Frenkel, M., Kamminga, C. E., and Willebrands, A. F., *J. Clin. Invest.*, **31**, 87 (1952)
282. Gross, J., and Pitt-Rivers, R., *Lancet*, **I**, 439 (1952)

283. Wiswell, J. G., and Asper, S. P., Jr., *J. Clin. Endocrinol. and Metabolism*, **13**, 851 (1953)
284. Gross, J., and Pitt-Rivers, R., *Lancet*, **I**, 593 (1952)
285. Plotz, C. M., Knowlton, A. I., and Ragan, C., *Am. J. Med.*, **13**, 597 (1952)
286. Knowlton, A. I., *Bull. N. Y. Acad. Med.*, **29**, 441 (1953)
287. Starr, A. M., *J. Clin. Endocrinol. and Metabolism*, **12**, 502 (1952)
288. Trethowan, W. H., and Cobb, S., *Arch. Neurol. Psychiat.*, **67**, 283 (1952)
289. Clark, D. E., Rule, J. H., Trippel, O. H., and Cofrin, D. A., *J. Am. Med. Assoc.*, **150**, 1269 (1952)
290. McGavack, T. H., *Med. Clin. N. Amer.*, 603 (1952)
291. Wilkins, L., and Ravitch, M. M., *Pediatrics*, **9**, 671 (1952)
292. Forbes, A. P., and Albright, F., *J. Clin. Endocrinol.*, **11**, 926 (1951)
293. Irwin, G. W., VanVactor, H. D., and Morris, M. S., *J. Am. Med. Assoc.*, **149**, 1637 (1952)
294. McCullagh, E. P., *Ann. Internal Med.*, **37**, 739 (1952)
295. Migeon, C. J., and Gardner, L. I., *J. Clin. Endocrinol. and Metabolism*, **12**, 1513 (1952)
296. Gardner, L. I., and Migeon, C. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 1117 (1952)
297. Walters, W., *Lancet*, **I**, 221 (1952)
298. Wilkins, L., Gardner, L. I., Crigler, J. F., Jr., Silverman, S. H., and Migeon, C. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 257 (1952)
299. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 277 (1952)
300. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 1015 (1952)
301. Crigler, J. F., Jr., Silverman, S. H., and Wilkins, L., *Pediatrics*, **10**, 397 (1952)
302. Bentinck, R. C., Hinman, F., Lisser, H., and Traut, H. F., *Postgrad. Med.* **11**, 301 (1952)
303. Rollman, H., Petit, D. W., and Starr, P. *J. Lab. Clin. Med.*, **39**, 697 (1952)
304. Gabrilove, J. L., *J. Clin. Invest.*, **31**, 360 (1952)
305. Tala, P., *Acta Endocrinol.*, *Suppl. 9* (1952)
306. Thompson, W. O., *J. Clin. Endocrinol. and Metabolism*, **12**, 130 (1952)
307. Kendrich, R. L., Balls, K., and Rose, E., *Arch. Internal Med.*, **89**, 368 (1952)
308. Myrke, J., *Acta Endocrinol.*, **10**, 233 (1952)
309. Allen, W. M., Hayward, S. J., and Pinto, A., *J. Clin. Endocrinol.*, **10**, 54 (1950)
310. Patterson, J., *Lancet*, **II**, 580 (1947)
311. Ronzoni, E., *J. Clin. Endocrinol. and Metabolism*, **12**, 527 (1952)
312. Kinsell, L. W., and Lisser, H., *J. Clin. Endocrinol. and Metabolism*, **12**, 50 (1952)
313. Robbins, J., Rall, J. E., Becker, D. V., and Rawson, R. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 856 (1952)
314. Carter, A. C., and Shorr, E., *J. Clin. Endocrinol. and Metabolism*, **12**, 1059 (1952)
315. Kelley, V. C., Ely, R. S., and Raile, R. B., *J. Clin. Endocrinol. and Metabolism*, **12**, 1140 (1952)
316. Venning, E. A., Pattee, C. J., McCall, F., and Browne, J. S. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 1409 (1952)
317. Gardner, L. I., and Migeon, C. J., *Helv. Paediat. Acta*, **6**, 465 (1951)

318. Robertson, J. D., and Kirkpatrick, H. F. W., *Brit. Med. J.*, **II**, 624 (1952)
319. Dohan, F. C., Rose, E., Eiman, J. W., Richardson, E. M., and Zintel, H., *J. Clin. Endocrinol. and Metabolism*, **13**, 415 (1953)
320. Schultz, A. L., and Jacobson, W. E., *J. Clin. Endocrinol. and Metabolism*, **12**, 1205 (1952)
321. Cope, O., *New England J. Med.*, **246**, 368, 408, 451 (1952)
322. Kark, R. M., and Muehrcke, R. C., *Lancet*, **I**, 1189 (1952)
323. Bruce, H. M., Parkes, A. S., and Perry, W. L. M., *Lancet*, **I**, 790 (1952)
324. Hamilton, H. B., and Werner, S. C., *J. Clin. Endocrinol. and Metabolism*, **12**, 1083 (1952)
325. Seed, L., and Jaffe, B., *J. Clin. Endocrinol. and Metabolism*, **13**, 107 (1953)
326. Casas, C. B., and Koppisch, E., *Endocrinology*, **51**, 322 (1952)
327. Goldberg, R. C., and Chaikoff, I. L., *Arch. Pathol.*, **53**, 22 (1952)
328. Crispell, K. R., Parson, W., and Sprinkle, P., *J. Clin. Endocrinol. and Metabolism*, **13**, 221 (1953)
329. Berte, S. J., *Ann. Internal Med.*, **38**, 28 (1953)
330. Thompson, W. O., *J. Clin. Endocrinol. and Metabolism*, **13**, 457 (1953)
331. Peterson, R. R., and Young, W. C., *Endocrinology*, **50**, 218 (1952)
332. Soffer, A., *J. Am. Med. Assoc.*, **148**, 339 (1952)
333. Bartels, E. C., *J. Clin. Endocrinol. and Metabolism*, **13**, 95 (1953)
334. Parson, W., Crispell, K. R., and Ebbert, A., Jr., *J. Clin. Invest.*, **31**, 548 (1952)
335. Jailer, J. W., Louchart, J., and Cahill, G. F., *J. Clin. Invest.*, **31**, 880 (1952)
336. Borst, J. G. C., ten Holt, S. P., de Vries, L. A., and Molyhausen, J. A., *Lancet*, **I**, 657 (1953)
337. Fisher, G., Epstein, D., and Paschkis, K. E., *J. Clin. Endocrinol. and Metabolism*, **12**, 1100 (1952)
338. Douglas, D., and Kennie, A. T., *Brit. Med. J.*, **II**, 1387 (1952)
339. Wilkins, L., *J. Pediat.*, **41**, 860 (1952)
340. Reilly, W. A., and Bayer, D. I., *J. Pediat.*, **40**, 714 (1952)
341. Swingle, W. W., Collins, E., Barlow, G., and Fedor, E., *Am. J. Physiol.*, **169**, 118 (1952)
342. Swingle, W. W., Perlmutt, J., Seay, P., and Collins, E., *Am. J. Physiol.*, **169**, 278 (1952)
343. Wolfson, W. Q., *Arch. Internal Med.*, **92**, 108 (1953)
344. Ingle, D. W., and Li, C. H., *Proc. Soc. Exptl. Biol. Med.*, **79**, 128 (1952)
345. Geschwind, I. I., and Li, C. H., *Endocrinology*, **50**, 226 (1952)
346. Geschwind, I. I., Reinhardt, W. O., and Li, C. H., *Nature*, **169**, 1061 (1952)
347. Raben, M. S., Rosenberg, I. N., and Astwood, E. B., *Federation Proc.*, **11**, 126 (1952)
348. Luetscher, J. A., Jr., and Johnson, B. B., *J. Clin. Invest.*, **32**, 585 (1953)
349. Freedberg, A. S., Kurland, G. S., Chamovitz, D. L., and Ureles, A. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 86 (1952)
350. Stanbury, J. B., Brownell, G. L., Riggs, D. S., Perinetti, H., del Castillo, E., and Itoiz, J., *J. Clin. Endocrinol. and Metabolism*, **12**, 191 (1952)
351. Lazarow, A., *Diabetes*, **1**, 171 (1952)
352. Kochakian, C. D., and Robertson, E. J., *J. Biol. Chem.*, **190**, 495 (1951)
353. Ingle, D. J., Prestrud, M. C., and Nezamis, J. A., *Am. J. Physiol.*, **166**, 171 (1951)
354. Conn, J. W., Louis, L. H., and Johnston, M. W., *Science*, **109**, 279 (1949)

355. Balmain, J. H., Folley, S. J., and Glascock, F. F., *Nature*, **169**, 447 (1952)
356. Altman, K. I., Miller, L. L., and Bly, C. G., *Arch. Biochem. and Biophys.*, **31**, 329 (1951)
357. Kinsell, L. W., Margen, S., Michaels, G. D., Reiss, R., Frantz, F., and Carbone, J., *J. Clin. Invest.*, **30**, 1491 (1951)
358. Pierce, F. T., Jr., and Bloom, B., *Metabolism*, **1**, 163 (1952)
359. Bloom, B., and Pierce, F. T., Jr., *Metabolism*, **1**, 155 (1952)
360. Sonenberg, M., Keston, A. S., Money, W. L., and Rawson, R. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 1269 (1952)
361. Rosenman, R. H., Byers, S. O., and Friedman, M., *J. Clin. Endocrinol. and Metabolism*, **12**, 1287 (1952)
362. Lerman, J., Harington, C. R., and Means, J. H., *J. Clin. Endocrinol. and Metabolism*, **12**, 1306 (1952)
363. Werner, S. C., Hamilton, H., and Nemeth, M. R., *J. Clin. Endocrinol. and Metabolism*, **12**, 1349 (1952)
364. Brush, B. E., and Altland, J. K., *J. Clin. Endocrinol. and Metabolism*, **12**, 1380 (1952)
365. Cattell, R. B., Alford, A. W., and Bartels, E. C., *J. Clin. Endocrinol. and Metabolism*, **12**, 1389 (1952)
366. Danowski, T. S., Wirth, P., Brown, M., Hill, G. C., and Fetterman, G. H., *J. Clin. Endocrinol. and Metabolism*, **12**, 1454 (1952)
367. Benua, R. S., Albert, A., and Keating, F. R., Jr., *J. Clin. Endocrinol. and Metabolism*, **12**, 1461 (1952)
368. Money, W. L., Rall, J. E., and Rawson, R. W., *J. Clin. Endocrinol. and Metabolism*, **12**, 1493 (1952)
369. Werner, S. C., Hamilton, H., and Nemeth, N., *J. Clin. Endocrinol. and Metabolism*, **12**, 1561 (1952)
370. Sohval, A. R., Weiner, I., and Soffer, L. J., *J. Clin. Endocrinol. and Metabolism*, **12**, 1053 (1952)
371. Sohval, A. R., and Soffer, L. J., *J. Clin. Endocrinol.*, **11**, 677 (1951)
372. Foreign letter, *J. Am. Med. Assoc.*, **145**, 341 (1951)
373. Blackburn, C. M., McConahey, W. M., and Keating, F. R., Jr., *J. Clin. Endocrinol. and Metabolism*, **13**, 852 (1953)
374. Lindsay, S., Dailey, M. E., Friedlander, J., Yee, G., and Soley, M. H., *J. Clin. Endocrinol. and Metabolism*, **12**, 1578 (1952)
375. Wyngaarden, J. B., Wright, B. M., and Ways, P., *Endocrinology*, **50**, 537 (1952)
376. Koneff, A. A., Van Dyke, D. C., and Evans, H. E., *Endocrinology*, **51**, 249 (1952)
377. Silver, S., Fieber, M. H., and Yohalem, S. B., *Am. J. Med.*, **13**, 725 (1952)
378. Weiss, S. B., Marx, L., and Marx, W., *Endocrinology*, **50**, 192 (1952)
379. Botkin, A. L., Praytor, E. H., Austing, M. E., and Jensen, H., *Endocrinology*, **50**, 550 (1952)
380. Maloof, F., Dobyns, B. M., and Vickery, A. L., *Endocrinology*, **50**, 612 (1952)
381. Bongiovanni, A. M., *J. Clin. Endocrinol. and Metabolism*, **13**, 847 (1953)
382. Hazashida, T., and Li, C. H., *Endocrinology*, **50**, 187 (1952)
383. Soffer, L. J., Gabrilove, J. L., and Wolf, B. S., *J. Clin. Endocrinol. and Metabolism*, **12**, 690 (1952)
384. Maasen, A. P., *Acta Endocrinol.*, **9**, 141 (1952)

385. Kretchmer, A. L., Gomberg, H. J., Wezant, O. E., and Bethell, F. H., *Endocrinology*, **51**, 59 (1952)

386. Hall, C. E., Hall, O., and McCleskey, O., *Acta Endocrinol.*, **9**, 199 (1952)

387. Reinhardt, W. O., Geschwind, I. I., Porath, J. O., and Li, C. H., *Proc. Soc. Exptl. Biol. Med.*, **80**, 439 (1952)

388. Done, A. K., Ely, R. S., Raile, R. B., and Kelley, V. C., *Proc. Soc. Exptl. Biol. Med.*, **81**, 667 (1952)

389. Kelley, V. C., Ely, R. S., Raile, R. B., and Bray, P. F., *Proc. Soc. Exptl. Biol. Med.*, **81**, 611 (1952)

390. Peterson, D. H., and Murray, H. C., *J. Am. Chem. Soc.*, **74**, 1871 (1952)

391. Lukes, R. M., *Merck Rept.*, **62**, 27 (1953)

392. Burn, J. H., *The Formation of Adrenaline in the Body*, (The University, Nottingham, England, 1951)

393. Goldenberg, M., *Am. J. Med.*, **10**, 627 (1951)

394. Shapiro, A. P., Harrison, H. M., Hoffman, M. S., and Ferris, E. B., *Am. J. Med.*, **10**, 115 (1951)

395. Graham, J. B., *Surg. Gynecol. Obstet.* (*Interm. Abstr. Surg.*), **92**, 105 (1951)

396. Rothschild, I., and Rapport, A. L., *Endocrinology*, **50**, 580 (1950)

397. Shepherd, D. M., and Wisl, G. B., *Brit. J. Pharmacol.*, **6**, 665)1951)

398. Gifford, R., Jr., Roth, G. M., and Kvale, W. F., *J. Am. Med. Assoc.*, **149**, 1628 (1952)

399. Effersoe, P., Gertz, T. C., and Lund, A., *Acta Chir. Scand.*, **103**, 43 (1952)

400. Roth, G. M., Dockerty, M. B., and Hightower, N. C., Jr., *Surg. Clin. North Amer.*, 1065 (1952)

401. Stokes, E. H., *Med. J. Australia*, **I**, 144 (1952)

402. Neill, C. A., and Smith, G., *Arch. Disease Childhood*, **27**, 286 (1952)

403. Davies, J. U. S. A., *Brit. Med. J.*, **II**, 77 (1952)

404. Rotherwick, N. O., *Ann. Internal Med.*, **36**, 157 (1952)

405. Young, W. C., Rayner, B., Peterson, R. R., and Brown, M. M., *Endocrinology*, **51**, 12 (1952)

406. Swan, H. J. C., *Brit. Med. J.*, **I**, 1003 (1952)

407. Peterson, R. R., Webster, R. C., Rayner, B., Young, W. C., *Endocrinology*, **51**, 504 (1952)

408. Perlmutter, M., Weisenfeld, S., Slater, S., and Wallace, E. L., *J. Clin. Endocrinol. and Metabolism*, **12**, 208 (1952)

409. Leblond, C. P., and Eartly, H., *Endocrinology*, **51**, 26 (1952)

410. Rupp, J. J., *Endocrinology*, **51**, 306 (1952)

411. Cope, O., Labbe, J. P., Raker, J. W., and Bland, E. F., *J. Clin. Endocrinol. and Metabolism*, **12**, 875 (1953)

412. Glushien, A. S., Mansuy, M. M., and Littman, D. S., *Amer. J. Med.*, **14**, 318 (1953)

413. Dent, C. E., *J. Bone and Joint Surg.*, **34B**, 266 (1952)

414. Fanconi, G., and Girardet, P., *Helvet. Paediat. Acta*, **7**, 14 (1952)

415. Steinberg, H., and Waldron, B. R., *Medicine*, **31**, 133 (1952)

416. Rand, G. G., Riggs, D. S., and Talbot, N. B., *Endocrinology*, **51**, 322 (1952)

417. Simpson, J. A., *Brain*, **75**, 76 (1952)

418. Crispell, K. R., and Parson, W., *J. Clin. Endocrinol. and Metabolism*, **12**, 881 (1952)

419. Schmith, K., and Faber, V., *Acta Endocrinol.*, **9**, 365 (1952)

420. Wijnbladh, H., *Acta Endocrinol.*, **10,** 105 (1952)
421. Tighe, W. J., *J. Clin. Endocrinol. and Metabolism*, **12,** 1220 (1952)
422. Freedberg, A. S., Kurland, M. S., and Blumgart, A. L., *J. Clin. Endocrinol. and Metabolism*, **12,** 1315 (1952)
423. Blohm, R. W., Jr., Wurl, O. A., Gillespie, J. O., and Escamilla, R. F., *J. Clin. Endocrinol. and Metabolism*, **13,** 519 (1953)
424. Klein, R., and Gow, R. C., *J. Clin. Endocrinol. and Metabolism*, **13,** 271 (1953)
425. Howard, J. E., Hopkins, T. R., and Connor, T. B., *J. Clin. Endocrinol. and Metabolism*, **12,** 927 (1952)
426. Albright, F., *Bull. N. Y. Acad. Med.*, **29,** 5 (1953)
427. Woolner, L. B., Keating, F. R., Jr., and Black, B. M., *Cancer*, **5,** 1069 (1952)
428. Murphy, R., Hurxthal, L. N., and Bell, G. O., *Arch. Internal Med.*, **89,** 738 (1952)
429. Goldberg, R. C., and Chaikoff, I. L., *Endocrinology*, **50,** 115 (1952)
430. Park, W. D., and Swann, P. G., *Brit. Med. J.*, **II,** 1185 (1952)
431. Albert, A., and Keating, F. R., Jr., *Endocrinology*, **51,** 427 (1952)
432. Albright, F., Henneman, P., Benedick, P. H., and Forbes, A. P., *J. Clin. Endocrinol. and Metabolism*, **13,** 860 (1953)
433. Stewart, G. S., and Bowen, H. F., *Endocrinology*, **51,** 80 (1952)

ALLERGY[1,2]

By B. N. Halpern and B. Benacerraf

Hospital Broussais-La Charité, Paris, France

During the past year a large volume of literature on allergy and immunology has been accumulated. It is impossible for evident reasons to quote all studies published, and it is not our intention to abstract each article entirely. This procedure would not fit well into the spirit of this book and would hardly satisfy the majority of our readers. Rather we will try to be selective and to choose a limited number of problems capable, in full evolution, of informing one on the new trends and the new developments in allergy. The progress in allergy, more than in other branches of medicine, is essentially based on progress in immunology, biochemistry, and pharmacology. In writing this review these considerations have been kept in mind.

Two important international scientific meetings, the celebration of the fiftieth anniversary of the discovery of anaphylaxis held in Paris, and the second European Congress of Allergy held in Copenhagen, brought together scientists and allergists and offered the opportunity of bringing up to date certain important problems. Portier (1) who described with Charles Richet in 1902 the basic phenomenon of anaphylaxis recalled the circumstances of the birth of this considerable discovery, and Dale (2) developed the actual conceptions of the mechanism of anaphylaxis and allergy in general.

In Copenhagen, MacDowall (3) referred to new theories on the action of antigens and histamine on the cells, based on recent personal experiments. According to the London physiologist, the Na/K imbalance is the essential phenonemon in hypersensitivity and tachyphylaxis. During activity, smooth muscles, like other tissues, take up sodium, and when they do so, they become less excitable. At this stage a lowering of the sodium concentration or an excess of potassium restitutes their activity to the cells. Organs, refractory after the first addition of a large dose of histamine (tachyphylaxis) recover their sensitivity to small doses of the drug in a low sodium medium especially with a small amount of extra potassium. It is suggested by the authors that in allergic states the body is deficient in sodium as a result of adrenal insufficiency, and the smooth muscles become abnormally excitable. They react to histamine with abnormal violence. The adrenal hormones mobilizing the potassium and retaining the sodium restore, through this electrolytic shift, the normal excitability of the cells. The action of ACTH[2] and cortisone in respiratory allergy has been discussed by Vallery-Radot (4) and their effect on dermatological conditions by Nilzen (5). The

---

[1] The survey of the literature pertaining to this review was concluded in July, 1953.

[2] The following abbreviation was used in this chapter: ACTH (adrenocorticotropin).

problems of infectious allergy [Bordet (6)] and of the role of infections in allergy of the respiratory tract have also been discussed (7, 8, 9).

IMMUNOLOGY

Antigens.—There are still controversial results on the nature of pollen antigens. Abramson (9) had previously isolated by electrophoretic technique the main active components of timothy pollen in a practically pure state. Recently Augustin (10) reported that, by ultrafiltration followed by iso-electric precipitation and salt fractionation, she was able to isolate from timothy extract highly purified and even crystallized antigens. The molecular weight of this crystallized protein is 14,000. With this antigen, potent precipitating antisera in rabbits and guinea pigs could be prepared.

According to the work of Hoet *et al.*, the various grass pollen extracts contain, besides common cross reacting antigens, a mosaic of antigens characteristic for each pollen. This could be demonstrated by preparing rabbit antisera with three (11) to six (12) different pollens and by studying immunologically the action of these sera on tanned red cells coated with antigen. [Boyden (13)]. This experimental quantitative method can be used for standardizing the allergenic activity of pollen extracts.

Organ antigenicity is of considerable interest for the pathogenesis of many diseases. Concerning the allergenicity of kidney extracts, Hill & Cruikshank (14) report that the fluorescein labeled antibodies prepared against homogenate of whole rat kidney react with the basement membrane of the glomeruli and also with the cytoplasm of the convoluted tubules. The antibodies prepared against purified glomeruli and lung extracts fix themselves selectively on the basement membrane of the glomeruli. This suggests the existence in the kidney homogenate of at least two distinct antigens: one originating from the glomeruli and another from the tubules. In another domain Crampton & Haurowitz (15) completing their investigations on the fate of injected antigens report that the pattern of distribution of the allergen in the tissues depends on the way and the size of injections. When small quantities of antigen are injected intravenously, the labeled iodovalbumin is retained in the lungs, and a small amount is found in the liver and spleen. Most of the antigen present in the liver and the spleen is located intracellularly in the cytoplasmic granules containing the mitochondrial fractions. The importance of this observation is brought out by the role which is attributed now to the mitochondria in the synthesis of proteins.

The resistance of the antigens to physical agents is very different from one protein to another. By the "dual injection passive transfer," Ratner *et al.* (16, 17, 18) established that egg albumin and egg globulin lose their antigenicity when submitted to moist heat, while fish proteins remain highly allergenic. In oranges, the seeds contain a powerful antigen, but the refined oil of peanut is devoid of allergenic properties.

Antibodies.—The site of the production of antibodies seems to depend upon the route of administration of the antigen. However, the role of the

spleen should be emphasized. Fragments of spleen, bone marrow, and lymph nodes of rabbits immunized with paratyphoid B vaccine are able to produce antibodies when cultivated in roller tubes for 24 hr. while under the same conditions liver or thymus do not produce antibodies. The red pulp of the spleen is the most potent producer of antibodies [Thorbecke & Keunig (19)]. In totally irradiated animals, shielding of the spleen maintains good antibody production provided that antigen is given intravenously [Wissler *et al.* (20)].

On the other hand, the local state of inflammation has a definite effect on the amount of antibodies produced: the presence of *Mycobacterium tuberculosum* responsible for local granuloma formation and hyperplasia is essential to obtain high and prolonged antibody levels in guinea pigs injected subcutaneously with ovalbumin together with adjuvants (21). The intradermal route of injections of a suspension of spinal cord combined with adjuvants is more effective in promoting allergic encephalomyelitis than the subcutaneous way (22).

The effect of the adrenal hormones on the rate of antibody production inspired several important studies. In general, the authors confirm that antibody production is depressed by ACTH and cortisone; this effect is reported in animals either in the course of active sensitization (23 to 26) or after the anamnestic response (27, 28).

In their experiments, Halpern *et al.* (27) studied the effect of cortisone on the level of precipitins in rabbits sensitized against ovalbumin during the period which follows the challenging injection of a neutralizing dose of antigen. It was found that in the first 48 hr. following the injection of antigen, the level of the precipitins in the sera of the treated animals was significantly higher than in the control animals. After the third day, on the contrary, the level of antibodies in the treated animals was found to be lower than in the controls.

The early increase in the serum antibody levels is attributed to the release of antibodies from the lymphatic tissue under the action of the hormone. This view is supported by the considerable lysis of lymphocytes observed in the blood and lymph nodes. The lower antibody levels observed later in treated animals are probably attributable to an inhibition by the hormone of antibody production.

Wiener (29) draws from his great knowledge of the Rh factor certain applications to the domain of allergy. He states that univalent antibodies are apparently involved in the immunity against pathogenic germs, while the bivalent (precipitating or agglutinating) antibodies play the essential role in allergic phenomena. When the antigen is repeatedly injected in the hyposensitization treatment, not only does the titer of the antibodies tend to rise but the quality changes and the amount of univalent (blocking) antibodies becomes prevalent. The allergic manifestations result from interaction between the antigen and bivalent antibodies, while its association with the blocking antibodies is symptomless and beneficial.

On the other hand, Kuhns & Pappenheimer (30, 31) have previously shown, using the diphtheria toxin-antitoxin system, that individuals with an allergic past produce predominantly a nonprecipitable antitoxin which behaves physically and immunologically very much like human reagins. This suggests that the diphtheria toxin-antitoxin system may be used as a pattern for the study of the hay fever allergy.

However, the essential nature and the intimate difference between the precipitating and nonprecipitating antibodies is still a matter for discussion. According to Bordet (32), the difference is only of a physical nature since simple physical procedures such as heating and delipidation may transform a precipitating system into a nonprecipitating antibody. The work of Sherman et al. (33) concerning human skin sensitization with nonprecipitable rabbit antiovalbumin could not be confirmed by Vaughan & Kabat (34) who attribute the phenomenon observed by Sherman to one or more antibodies produced by the rabbit against impurities contained in crystallized ovalbumin other than conalbumin, ovomucoid, and lysosime. The lysis of white cells during the antigen-antibody reaction observed by Waksman (35) is attributed by him to the nonprecipitable antibody. Malkiel & Feinberg (36), studying antibody production in humans, failed to obtain in normal nonallergic human individuals antibody response after prolonged treatment with ragweed extracts. On the contrary, in individuals affected with hay fever a low antibody titer was found in only $\frac{1}{3}$ of the untreated patients, but all the treated patients produced antibodies in high titer. However, there was no relation between the amount of antibodies and the clinical relief(37). In cases of spontaneous sensitivity to egg white, Grabar et al. (38) using Boyden's technique were able to demonstrate agglutinating antibodies against ovalbumin. The level of antibodies does not seem to be distributed evenly in the tissues, since in the aqueous humour the titer of antibodies was found to be 10 to 350 times less than in the blood (39).

The nonvascular corneal parenchyme differs from other tissues with respect to sensitization. The corneal sensitization can be produced only when the antigen is injected locally, but a locally sensitized cornea does not react when the antigen is administered systemically (40).

As to the physical properties of the allergic humoral antibodies, the recent data are in agreement with the view that they are found principally in the β-globulin fraction either by electrophoretic convection or alcohol fractionation (41, 42, 43). Loveless (44) showed also that the allergic antibodies, both sensitizing and blocking, are not significantly altered by ultraviolet irradiations.

These findings are in apparent contradiction with those of Hanan (44a) who showed that the ultraviolet irradiation of a rabbit antiserum decreases not only its precipitability but also its capacity of sensitizing guinea pigs. The property to sensitize guinea pigs for anaphylactic shock is completely lost even before the precipitability of the serum is affected.

ANAPHYLAXIS

Burrage & Irwin (45) performed direct microscopic observation by transilluminations of the intrahepatic circulation in anesthetized and sensitized guinea pigs during anaphylactic shock with a technique similar to that used by Knisely. During the anaphylactic shock the arterioles were seen to contract, the sphincters of the sinusoids at the central veinules shut off, and the sinusoids became engorged with blood. Finally the blood flow in the portal veinules ceased. The consequence was an accumulation of a considerable amount of blood in the liver leading to a considerable enlargement of the organ. These findings confirm the important role of the vessels in anaphylactic reactions.

As for histamine toxicity, treatment of mice with pertussis vaccine increases their sensitivity to anaphylactic shock (45a). The mechanism of the exaltation of this sensitivity which is observed in mice is still unknown. Cortisone and antihistaminics are able to decrease both histamine and anaphylactic hypersensitivity of the pertussis treated mice (46).

Cutaneous anaphylaxis in various species of animals has been thoroughly studied by Ovary and his co-workers. The technique used was described previously by Biozzi, Ovary & Mené (47), and it consists of the intradermal administration of antiserum and the subsequent injection of the antigen together with a blue dye intravenously. A positive reaction is indicated by the appearance of a blue spot at the site of the injection of the antiserum, easily visible on the reflected skin about 10 min. after the injection of the antigen. The minimum amount of rabbit antiovalbumin which determines a positive reaction in guinea pigs is as small as 0.003 μg. (48). This cutaneous anaphylaxis, as to the general conditions: amount of antibody, type of antibody, latent period, action of antihistaminics, etc., is identical to the phenomenon of systemic anaphylaxis (49, 50, 51, 53). The quantity of antibodies required to sensitize rat's skin is about 1000 times more than for guinea pigs (52).

With this technique, it has been shown by Biozzi, Halpern & Benacerraf (54), that local or intradermal application of various vasoactive irritants such as histamine in minute doses, heat, distilled water, etc. determines a considerably more rapid fixation of the antibodies at the site treated. These observations may afford an explanation for certain problems concerning the electivity of "shock organs" in clinical allergy. The recent findings confirm definitely that the Arthus phenomenon depends exclusively, as it has been previously reported by Benacerraf & Kabat (54a), on circulatory precipitins (55, 56).

Many workers were concerned with the Schwartzman phenomenon, and new facts concerning its mechanism have been reported. Previous injection of particulate matter such as thorotrast or trypan blue, sensitize rabbits so that generalized or local reaction can be produced with a simple injection of meningococcal toxin (57, 58, 59). This exaltation of sensitivity is inter-

preted by the authors as being conditioned by a blockade of the reticulo-endothelial system. The effect of nitrogen mustard which inhibits the phenomenon through the depression of circulating leucocytes is prevented by cysteine. This aminoacid combats the leucopenic effect of nitrogen mustard (60).

Both local or general Schwartzman phenomena are inhibited by heparin injected intravenously or locally, provided that doses administered are high enough to cause a complete incoagulability of the blood, in spite of the fact that heparin does not interfere with the concomitant leucopenia and the toxicity of the toxin (61, 62).

The study of the action of cortisone and ACTH on anaphylactic shock leads to competing results. Germuth *et al.* (23), in confirming previous findings, were unable to protect guinea pigs with those hormones against either active or passive anaphylaxis. Dews & Code (25) found that cortisone reduces the hypersensitivity of adrenalectomized rats to anaphylaxis. However, Herxheimer *et al.* (63) report partial protection by cortisone of guinea pigs against anaphylactic reactions, and Feinberg & Malkiel (64) noted that cortisone protects guinea pigs against anaphylactic asthma. ACTH and cortisone suppress the renal lesions observed in rabbits after a single injection of beef gamma globulins. This action of the hormone was correlated with the lack of complement drop and a depression of antibody production (65). The intradermal allergic reaction to an atopen seems to be decreased by a single injection of ACTH (67).

With respect to the mechanism of action of cortisone on cellular hypersensitivity, it has been shown by Leahy & Morgan (66) that the pretreatment with cortisone of splenic macrophages of tuberculous guinea pigs renders them refractory to the damaging action of P.P.D. (purified protein derivative).

HISTAMINE AND HISTAMINE LIBERATORS

The role of histamine in allergic and anaphylactic reactions is still open to discussion. The recent discovery of histamine liberators gave a new stimulus to researches in this field. It will be seen from the work reviewed below that the syndromes produced by histamine liberators are characterized by symptoms strikingly similar to those found in allergic conditions. The antihistaminics inhibit the manifestations produced by histamine liberators, and also cortisone is able to reduce the effect of histamine liberators in certain conditions. The conclusions drawn from these observations may provide one with a better understanding of the pathogenesis of clinical allergy and of the effects of therapeutic agents on these conditions.

A certain number of substances are now known to act as histamine liberators. Some of them, such as compound 48/80 studied by Paton (a product of condensation of *p*-methoxy-phenyl-ethyl-methylamine with formaldehyde) are active in a wide range of animal species (67a, 68). Others belonging chemically to natural or synthetic high molecular weight polymers

act selectively on different animal species (69 to 72). The common symptoms produced by these substances are characterized by: erythema, edema either generalized or local (depending upon the route of administration), intense itching, vasodilatation and hypotension, gastric hypersecretion, and symptoms of shock such as hemoconcentration, hypothermia, and collapse. These symptoms can be elicited by compound 48/80 in dogs, cats, rats, guinea pigs (68, 73). The polymers such as dextran, ovomucoid (70, 71, 72), and globin (74) (extracted from red cells) are active only in rats, while polyvinyl-pyrolidone produces the pathological symptoms in dogs only (72). All these symptoms with the exception of gastric hypersecretion are inhibited completely by antihistaminics (72, 75).

Adrenalectomy renders the animals considerably more sensitive to histamine liberators (72, 74, 75) just as they do with respect to histamine (77) and anaphylactic shock (25).

The adrenal hormones and particularly cortisone and epinephrine (adrenaline), and even more the association of both hormones, restore the sensitivity of adrenalectomized animals to the normal level (76, 77).

That the histamine liberators act through a release of endogenous histamine responsible for the symptoms observed is evidenced by a simultaneous increase of histamine concentration in the plasma (78) and by a concomitant depletion of the tissular histamine (73). These substances are also able to release histamine from tissues *in vitro* (79, 80). Through the administration of an appropriate dose of histamine liberators it is possible to cause a more or less complete depletion of tissue histamine. Corresponding to this depletion of tissue histamine the animals are free from symptoms on subsequent injection of histamine liberators (73). It has been shown by Halpern *et al.* (81) that the time of reconstitution of the skin histamine stock in rats after its depletion by dextran is of about four to six days. Cortisone administered after the depletion of histamine seems to delay considerably the return of normal reactivity of the skin to histamine liberators, while DOCA (desoxycorticosterone acetate) does not interfere with this process (81). Similar observations were made by Goth *et al.* (82) on dogs with another histamine liberator, one of the "Tweens." These authors claim also that animals whose histamine has been depleted by anaphylactic shock were partially protected against passive anaphylaxis when treated with cortisone. Although these problems are at present time intensely investigated by several teams of workers some definite conclusions can be drawn especially with respect to the mechanism of action of cortisone in anaphylactic-like syndromes. The fundamental feature of all these disorders is a vascular injury: vasoparalysis, increase of the permeability of the capillaries to proteins and dyes, and general depression of the small vessels. This fundamental vascular feature can be observed either locally in inflammatory lesions or systemically in other conditions such as histaminic, hemorrhagic, or traumatic shock (83). It is well known that adrenalectomy increases the severity of all these syndromes probably through the same mechanism. What may be this common mecha-

nism? The answer is that the small vessels without adrenal hormonal secretion lose their normal reactivity and tonicity. Epinephrine, which is a potent vasotonic substance, is not able alone to restore the tonus of the vessels of the adrenalectomized animals in a state of shock (84, 85). The administration of cortisone and to a certain extent of DOCA together with epinephrine can remedy to this state. These results suggest that cortisone plays a very important role in the maintenance of the tonus of the peripheral circulation (74, 84 to 87). From the experiments performed with histamine liberators the evidence can be also drawn that cortisone interferes with histamine synthesis in the tissues. It seems, however, that when minute doses of exogenous histamine are administered, its fixation and metabolism remain unaffected by adrenalectomy (88). According to Grob (89), ACTH and cortisone do affect the renal excretion and cellular utilization of histidine.

CLINICAL ALLERGY

The problem of the fundamental status allergicus has challenged many authors. As can be deduced from the experimental evidences discussed above, outside of the immunological aspect, the common features of the allergic symptoms appear to depend upon a terrain of abnormal vascular reactivity which is controlled through hormonal function. Evidence has been brought by several authors for abnormal capillary permeability in allergic patients. These authors have shown that the capillaries of allergic individuals are abnormally permeable to fluorescein (90) as well as to plasma proteins (92).

The dramatic therapeutic results obtained with ACTH and cortisone have led to investigations of whether allergic patients present abnormal functions of the hypophysis or of the adrenals. Such works have dealt generally with the excretion of the ketosteroids (91, 93) and with studies on the responses to glandular stimulating or to stressing agents (93 to 96). The results reported so far are controversial and do not lead to a definite conclusion as to the adequacy of the hormonal function in allergic individuals, in spite of greater evidence that certain responses in allergic patients are altered.

The hormonal imbalance during pregnancy is probably responsible for the well known changes in asthma observed during this state. Up to now it is impossible to understand why certain women are benefited and others worsened by their pregnancies (97).

The hereditary factors in allergy have always been considered of foremost importance, and we would like to point out the remarkable and considerable work made by Schwartz on the genetics of bronchial asthma (97a).

The observations of Bowen (98) on 59 cases of monoplacental twins seen in over 15 years show that in 52 out of 59 cases the allergic condition existed in only one twin. In only two cases there was bilateral allergy of similar pattern.

Respiratory allergy.—A good review of the relations between upper respiratory allergy and bronchial asthma has been written by Hampsey (99).

The histamine content of mucous membranes of the nose is not significantly different in normal and allergic patients. The findings of eosinophils in the nasal smear is a good presumptive evidence of nasal allergy (100).

Continuing their investigations on the mechanism of experimental asthma, Noelpp & Noelpp-Eschenhaggen (101) found a great discrepancy between the air resistance in the bronchial tree and the energy developed for breathing during anaphylactic asthma. As they did not find any special changes in the intrinsic tonus of the respiratory muscles, they came to the conclusion that changes in the elastic and viscous properties of the lung tissue rather than the bronchospasm are responsible for the ventilatory difficulties in asthmatic conditions.

The importance of an organic lesion of the bronchi as an etiological factor of asthma has been emphasized by Overholt *et al.* (102); by the removal of bronchiectatic lesions in asthmatic patients, 20 out of 26 patients were greatly improved. Gutman (103) recently emphasized that the auscultation of the supraclavicular fossa allows one to detect residual signs of asthma in doubtful cases.

Attempts have been made to use exposure to aerosols of antigen as a provocative test for detecting the etiological agent of asthma (104, 105). Exposure of asthmatic patients to aerosols of allergens may produce either an immediate respiratory reaction or a later attack. It seems that this delayed respiratory reaction obtained mostly with house dust is equivalent to the skin delayed reaction (105). The excellent results of allergic hyposensitization in asthma of children are confirmed by the results of Unger *et al.* (106).

There is no outstanding development in the treatment of asthma. ACTH and cortisone continue to be the basic treatment of status asthmaticus and of intractable asthma. Good results are reported by all authors (107 to 111). Observations of prolonged treatment with cortisone for more than one year proves that this drug can be administered for a long period of time. The chief side effects reported were: gain in weight, hypertension, and recurrent respiratory infections (110). Association with antibiotics is often advisable (107, 112). A contributory work to the pathogenesis of Loeffler's syndrome is reported by Esselier *et al.* (113) who obtained blood eosinophilia and transient pulmonary shadows after the injection of vegetable oils in animals as well as in humans. These experiments provide an explanation of the Loeffler's syndrome observed in humans after injections of drugs in an oily vehicle.

Urticaria.—A thorough study of causes of angioneurotic edema was carried out in 132 patients covering a nine year period by Bruun (114). In 55 per cent of the cases unquestionable allergic etiology could be demonstrated. In 18 per cent of the cases allergy was presumed and in 27 per cent no etiology could be found.

For the possible etiology of physical urticaria the good therapeutic effect of atropine and the habituation to acetylcholine suggest the important role played by acetylcholine in its pathogenesis (115).

Food allergy.—In food allergy the diagnosis of the etiologic agent remains a difficult problem in most cases. The difficulty is even increased by the fluctuation of the sensitivity of the skin according to the actual ingestion of the food (116). The sensitivity of the individuals is often attributed to a breakdown product of the ailment. But the trials with digested food give only infrequently positive results (117). Only careful history, confirmed by elimination diet, is of diagnostic value.

Allergy to gelatin, generally considered as nonallergenic, with positive passive transfer, has been reported (118).

Miscellaneous allergies.—The mechanism of the allergic purpura seems to be clarified by the work of Ackroyd (119). It is now established that Sedormid causes purpura through an immunological process. The drug combines with the platelets conferring upon them the property of weak antigens which then stimulate antibody production in a limited number of individuals. Patients with thrombocytopenia have been shown to possess these antibodies which cause lysis of platelets in the presence of complement. The capillary lesions in purpura are probably produced in a similar way as there is a common antigen for platelets and capillary endothelium. Two extensive reviews of haematologic allergic manifestations have been published (119, 120).

In migraine headaches electrocardiographic alterations of some importance concomitant with the attack were observed. The electrocardiographic changes disappeared together with the headache after injection of ergotamine (121).

Drug allergy.—An excellent and remarkable general review of drug allergy where each drug is indexed with its common symptomatic picture has been written by Brown (122).

Everybody should keep in mind that penicillin is potentially a dangerous drug which should not be prescribed for trivial conditions. Several fatalities from penicillin have been reported during the last few months by different investigators (123, 124, 125). This type of sensitivity is usually induced by repeated courses of penicillin treatment by topical applications in patients subject to other allergies. Fatalities to procaine have been also reported (126).

Allergic eczematous dermatitis.—The recent works indicate the possibility of existence of cellular antibodies in allergic contact dermatitis. Nilzen (127) reports successful transference of hypersensitivity to 2,4-dinitro-1-chlorobenzene through cellular peritoneal exudate in guinea pigs, even though the donors had been treated with cortisone.

Attempts at passive transfer of allergic eczematous sensitivity in men were made by several groups of investigators (128 to 131). They all agree that they failed to find any definite evidence that allergic contact sensitivity can be passively transferred from one human being to another. However, some of the recipients developed what appeared to be an accelerated active sensitization to the allergens with which they were tested (128, 129).

The number of substances to which individuals develop skin sensitivity

increases every day. The blame should be put upon the wide use of drugs and complex cosmetics by topical administration. Among them may be mentioned: antihistaminics (132, 133), rubber (134), the para substances (135), dental prosthetics (136), cement (137). The action of cortisone on this type of sensitivity is confirmed when this hormone is administered parenterally (138). However, cortisone is ineffective by local application (139). In the past months the striking effect of hydrocortisone (compound F) by local administration has been reported by several investigators and especially by Sulzberger & Smith (140) and by Goldman and co-workers (141). The previous application of compound F inhibits the diagnostic patch test reaction (142).

Several authors stress the importance of the coexistence of dermatitis with respiratory allergy as a result of inhalants. Desensitization treatment is very often effective and the dermatological condition disappears together with the respiratory symptoms (143, 144, 145).

Although the psychosomatic aspects of allergic conditions should be kept in mind (146 to 149) at the same time that the general medical care of the patients is being organized, our feeling is that it is wrong to give too much weight and credit to that sole aspect of modern therapeutics.

Therapeutics.—Some minor progress has been made in the symptomatic therapy of allergic disorders. Repository ACTH (150) and epinephrine (151) present some advantages as a result of their prolonged action. Advantages are claimed for a poorly soluble antigen hydrochloride for desensitization treatment (152). The systematic addition of antihistaminics to allergenic extracts is recommended by Jenkins (153). Good results are claimed by Wittich with antazoline (Antistine; dibistine) and tripelennamine (Pyribenzamine) in various allergic syndromes (154). A new antihistaminic was described by Rothlin & Cerletti (155) who claim that good results are obtained in association with calcium. According to Parish (156) the association of procaine with ascorbic acid affords symptomatic relief for itching in a variety of conditions.

Surveys of aeroallergens (pollens, molds) have been reported (157, 158).

Among the general studies dealing with the various phases of allergy we would like to mention the excellent review of pediatric allergy by Fontana (159) and especially the symposium on the "Bases of Allergic Reactions" of the Royal Society of Medicine in London under the charmanship of Professor Payling Wright where papers were presented by Goldschmidt, Feldberg, Marrack, Ackroyd, and Lowell (160).

Two books were published in the last year. One is a collection of the reports and papers presented at the First International Congress of Allergy held in Zurich in 1951 (161) and the second, *Clinical Allergy* by Hensel, is a substantial manual of clinical allergy (162).

LITERATURE CITED

1. Portier, P., *Acta Allergrol.*, **5,** 175–81 (1952)
2. Dale, H. H., *Acta Allergol.*, **5,** 191–206 (1952)
3. MacDowall, R. J. S., *Acta Allergol.*, **6,** Suppl. III, 7–12 (1953)
4. Pasteur Vallery-Radot, L., Milliez, P., and Laroche, C., *Acta Allergol.*, (In press)
5. Nilzen, A., *Acta Allergol.*, **6,** Suppl. III, 13–20, (1953)
6. Bordet, P., *Acta Allergol.* **6,** Suppl. III, 91–104 (1953)
7. Jimenez-Diaz, C., and Arjona, E., *Acta Allergol.*, **6,** Suppl. III, 105–142 (1953)
8. Spoutitch, V., and Danilovitch, V., *Acta Allergol.* **6,** Suppl. III, 143–56 (1953)
9. Abramson, H. A., Engel, M. G., and Moore, D. H., *J. Allergy*, **14,** 65 (1942)
10. Augustin, R., *Acta Allergol.*, **6,** 194–95 (1953)
11. Hoet, J. J., Mynors, L. S., and Coombs, R. R. A., *Acta Allergol.*, **5,** 239–54 (1952)
12. Gosselin, M. L., Mynors, L. S., Coombs, R. R. A., and Milner, F. H., *Acta Allergol.*, **6,** 96–102 (1953)
13. Boyden, S. V., *J. Exptl. Med.*, **93,** 107 (1951)
14. Hill, A. G. S., and Cruikshank, B., *Brit. J. Exptl. Pathol.*, **34,** 27 (1953)
15. Crampton, C. F., and Haurowitz, F., *J. Immunol.* **69,** 457 (1952)
16. Ratner, B., Untracht, S., and Collins-Williams, C., *Ann. Allergy*, **10,** 675–81 (1952)
17. Ratner, B., Aikman, H. L., and Thomas, J. S., *Ann. Allergy*, **10,** 682–89 (1952)
18. Ratner, B., Untracht, S., Collins-Williams, C. Malone, H. J., and Retsina, M., *Ann. Allergy*, **10,** 690–97 (1952)
19. Thorbecke, G. S., and Keunig, F. S., *J. Immunol.*, **70,** 129, (1953)
20. Wissler, R. W., Robson, M. S., Fitch, F., Nelson, W., and Jacobson, L. O., *J. Immunol.*, **70,** 374 (1953)
21. Fischel, E. E., Kabat, E. A., Stoerk, H. C., and Bezer, A. E., *J. Immunol.*, **69,** 611 (1952)
22. Lipton, M. M., and Freund, J., *J. Immunol.*, **70,** 326 (1953)
23. Germuth, F. G., Ottinger, B., and Oyana, J., *Proc. Soc. Exptl. Biol. Med.*, **80,** 188 (1952)
24. Malkiel, S., and Hargis, B. S., *J. Immunol.*, **69,** 217 (1952)
25. Dews, P., and Code, C., *J. Immunol.*, **70,** 199 (1953)
26. Moeschlin, S., Baguena, R., and Baguena, J., *Intern. Arch. Allergy Appl. Immunol.*, **4,** 83–100 (1953)
27. Halpern, B. N., Mauric, G., Holtzer, A., and Briot, M., *J. Allergy*, **23,** 303 (1952)
28. Fischel, E. E., Vaughan, J. M., and Photopoulos, C., *Proc. Soc. Exptl. Biol. Med.*, **81,** 344 (1952)
29. Wiener, A. S., *Ann. Allergy*, **10,** 535–54 (1952)
30. Kuhns, W. J., and Pappenheimer, A. M., *J. Exptl. Med.*, **95,** 363–74 (1952)
31. Kuhns, W. J., and Pappenheimer, A. M., *J. Exptl. Med.*, **95,** 375–92 (1952)
32. Bordet, P., *Acta Allergol.*, **6,** Suppl. III, 91–104 (1953)
33. Sherman, W. B., Menzel, A. E., and Seebohn, P. M., *J. Exptl. Med.*, **92,** 191 (1950)
34. Vaughan, J. H., and Kabat, E. A., *J. Exptl. Med.*, **97,** 821 (1953)
35. Waksman, B. H., *J. Immunol.*, **70,** 331 (1953)
36. Malkiel, S., and Feinberg, S. M., *J. Allergy*, **23,** 504 (1952)
37. Orlans, E. S., Rubinstein, L. J., and Marrack, J. R., *Acta Allergol.*, **6,** 33–43 (1953)
38. Grabar, M. P., Borduas, A., and Holtzer, A., *Acta Allergol.* **5,** 30 (1952)

39. Ovary, Z., and D'Ermo, F., *Boll. oculist*, **32**, 69 (1953)
40. Edmund, J., *Acta Allergol.*, **6**, 118–23 (1953)
41. Menzel, A. E. O., Kossler, W. R., Cooke, R. A., and Myers, P., *J. Allergy*, **23**, 483 (1952)
42. Loveless, H. M., and Cam., J. R., *Science*, **117**, 105 (1953)
43. Vaughan, J. H., Favour, C. B., and Jaffé, I. H., *J. Allergy*, **23**, 489 (1952)
44. Loveless, H. M., *J. Immunol.*, **69**, 539 (1952)
44a. Hanan, R., *J. Immunol.*, **69**, 41 (1952)
45. Burrage, W. S., and Irwin, J. W., *Ann. Allergy*, **11**, 137–42 (1953)
45a. Malkiel, S., and Hargis, B. J., *Proc. Soc. Exptl. Bicl. Med.*, **80**, 122 (1952)
46. Kind, L. S., *J. Allergy*, **24**, 52 (1953)
47. Biozzi, G., Ovary, Z., and Mené, G., *Rev. immunol.*, **12**, 320 (1948)
48. Ovary, Z., and Briot, M., *Ann. inst. Pasteur*, **81**, 670 (1951)
49. Ovary, Z., *Inter. Arch. Allergy Appl. Immunol.*, **3**, 162 (1952)
50. Ovary, Z., *Acta Allergol.*, **4**, 324 (1951)
51. Ovary, Z., and Bier, O. G., *Ann. inst. Pasteur*, **84**, 443 (1953)
52. Ovary, Z., *Inter. Arch. Allergy Appl. Immunol.*, **3**, 293 (1952)
53. Benacerraf, B., and Kabat, E. A., *J. Immunol.*, **64**, 517 (1949)
54. Biozzi, G., Halpern, B. N., and Benacerraf, B., *Acta Allergol.*, **6**, Suppl. III, 183 (1953)
54a. Benacerraf, B., and Kabat, E. A., *J. Immunol.*, **66**, 1–19 (1950)
55. Kuhns, W. J., *J. Exptl. Med.*, **97**, 903 (1953)
56. Ovary, Z., and Bier, O. G., *Proc. Soc. Exptl. Biol. Med.*, **81**, 584 (1952)
57. Good, R. A., and Lewis, T., *J. Exptl. Med.*, **96**, 605 (1952)
58. Good, R. A., and Lewis, T., *J. Exptl. Med.*, **96**, 625 (1952)
59. Bennett, I. L., *Proc. Soc. Exptl. Biol. Med.*, **81**, 248 (1952)
60. Bennett, I. L., and Cluff, L. E., *Proc. Soc. Exptl. Biol. Med.*, **81**, 304 (1952)
61. Cluff, L. E., and Berthrong, M., *Bull. Johns Hopkins Hosp.*, **92**, 353 (1953)
62. Good, R. A., and Thomas, L., *J. Exptl. Med.*, **97**, 871 (1953)
63. Herxheimer, H., Rosa, L., Telfer, T. P., Thornton, P. M., and West, T., *Acta Allergol.*, **5**, 214–21 (1952)
64. Feinberg, S. M., and Malkiel, S., *Proc. Soc. Exptl. Biol. Med.*, **81**, 104 (1952)
65. Moll, F. C., and Van Zandt Hawn, C., *J. Immunol.*, **70**, 441 (1953)
66. Leahy, R. A., and Morgan, H. R., *J. Exptl. Med.*, **96**, 549 (1952)
67. Bowman, K. L., Siegel, B. B., and Walter, M., *J. Allergy*, **23**, 130 (1952)
67a. Paton, W. D. M., *Brit. J. Pharmacol.*, **6**, 499 (1951)
68. Paton, W. D. M., and Schachter, M., *Brit. J. Pharmacol.* **6**, 509, (1951)
69. Selye, H., *Endocrinology*, **21**, 169 (1937)
70. Halpern, B. N., Benacerraf, B., and Briot, M., *Brit. J. Pharmacol.*, **7**, 287 (1952)
71. Halpern, B. N., and Briot, M., *Compt. rend. soc. Biol.*, **146**, 15, (1952)
72. Halpern, B. N., and Briot, M., *Acta Allergol.*, **6**, Suppl. III, 68 (1953)
73. Feldberg, W., and Talesnik, J., *J. Physiology*, **120**, 550 (1953)
74. Swingle, W. W., Fedor, E. J., Maxwell, R., Ben, M. and Barlow, G., *Am. J. Physiology*, **172**, 527 (1953)
75. Halpern, B. N., and Briot, M., *Compt. rend. soc. biol.*, **146**, 21 (1952)
76. Halpern, B. N., and Briot, M., *Acta Allergol.*, **5**, 257 (1952)
77. Halpern, B. N., Benacerraf, B., and Briot, M., *Proc. Soc. Exptl. Biol. Med.*, **79**, 37 (1952)
78. Halpern, B. N., and Briot, M., *Compt. rend. soc. biol.* (In press)

79. Halpern, B. N., and Briot, M., *Compt. rend. soc. biol.*, **146**, 1552 (1952)
80. Mongar, J. L., and Schild, H. O., *Brit. J. Pharmacol.*, **8**, 103 (1953)
81. Halpern, B. N., Biozzi, G., Briot, M., and Benacerraf, B., *Compt. rend. soc. biol.*, (In press)
82. Goth, A., Halman, J., and Koppenhaver, J. H., *Quart. Rev.. Allergy Appl. Immunol.*, **7**, 4 (1953)
83. Menkin, V., *Intern. Arch. Allergy Appl. Immunol.*, **4**, 131–68 (1953)
84. Halpern, B. N., Benacerraf, B., and Briot, M., *Brit. J. Pharmacol.*, **7**, 287 (1952)
85. Ramey, E. R., Goldstein, M. S., and Levin, R., *Am. J. Physiology*, **165**, 450 (1951)
86. Ashton, N., and Cook, C., *Brit. J. Explt. Pathol.*, **33**, 445 (1952)
87. Halpern, B. N., Biozzi, G., Benacerraf, B., and Briot, M., *Acta Allergol.*, **5**, 258 (1952)
88. Schayer, R. W., Smiley, P. E., and Kennedy, J., *Proc. Soc. Exptl. Biol. Med.*, **81**, 416 (1952)
89. Grob, D., *Bull. Johns Hopkins Hosp.*, **90**, 341 (1952)
90. Huber, A., *Intern. Arch. Allergy Appl. Immunol.*, **4**, 200–10 (1953)
91. Anderson, E., *Acta Allergol.*, **6**, 107 (1952)
92. Halpern, B. N., and Musso, G., (Unpublished data)
93. Quarles van Ufford, A., *Acta Allergol.*, **6**, Suppl. III, 48–54 (1953)
94. Dragstedt, P. J., *Acta Allergol.*, **6**, 503 (1953)
95. Jouge, de G. A., Veenland, B. M., Van Genns Heinberg, H., Leemhuis, A. P., Israël, A. A., and Orie, N. G., *Acta Allergol.*, **5**, 270–91 (1952)
96. Steinberg, T. H., and Zimmermann, M. C., *Arch. Dermatol. and Syphilol.*, **65**, 392 (1952)
97. Jensen, K., *Acta Allergol.* **6**, 44–53 (1953)
97a. Schwartz, M., *Acta Allergol.*, **5**, Suppl. II, 1–288 (1952)
98. Bowen, R., *J. Allergy*, **24**, 236 (1953)
99. Hampsey, J. W., *Ann. Allergy*, **10**, 727–31 (1952)
100. Baxter, J., and Bram, R., *J. Allergy*, **24**, 18 (1953)
101. Noelpp, B., and Noelpp-Eschenhaggen, I., *Intern. Arch. Allergy Appl. Immunol.*, **3**, 302–23 (1952)
102. Overholt, R. H., Walker, J. H. and Woods, F. M., *J. Am. Med. Assoc.*, **150**, 438 (1952)
103. Gutman, M. G., *J. Am. Med. Assoc.*, **151**, 1285 (1953)
104. Colldahl, H., *Acta Allergol.*, **5**, 133–50 (1952)
105. Herxeimer, H., *Intern. Arch. Allergy Appl. Immunol.*, **3**, 323–28 (1952)
106. Unger, L., Unger, A. H., and Wolf, A. A., *Ann. Allergy*, **10**, 574–81 (1952)
107. Pasteur Vallery-Radot, L., Laroche, C., Milliez, P., Domart, A., and Reiner, J. L., *Bull. mémoires soc. méd. hôp. Paris*, **68**, 319 (1952)
108. Lockey, S. D., Paul, J. D., Grosh, J. L., Griswold, A. S., and Stubb, D. S., *Ann. Allergy*, **10**, 592–604 (1952)
109. Lowell, F. C., Schiller, L. W., Leard, S. E., and Franklin, W., *J. Allergy*, **24**, 112 (1953)
110. Burrage, W. S., and Irwin, J. W., *New Engl. J. Med.* **248**, 679 (1953)
111. Castaigne, A., *Presse méd.*, **61**, 536, (1953)
112. Rosen, F. L., *Ann. Allergy*, **10**, 629–31 (1952)
113. Esselier, A. F., Martin, H. R., Morandi, L., and Wagner, K., *Intern. Arch. Allergy Appl. Immunol.*, **3**, 279–93 (1952)

114. Bruun, E., *J. Allergy*, **24**, 97 (1953)
115. Herlitz, G., *Intern. Arch. Allergy Appl. Immunol.*, **4**, 1–10 (1953)
116. Kremer, W., *Acta Allergol.*, **6**, 124 (1953)
117. Bloom, S., Markow, H., and Redner, B., *J. Allergy*, **24**, 64 (1953)
118. Mendez, R. L., and Hughes, H., *Acta Allergol.*, **5**, 230–38 (1952)
119. Ackroyd, J. F., *Am. J. Med.*, **14**, 605 (1953)
120. Reissner, E. H., *J. Allergy*, **23**, 550 (1952)
121. Langarrat, M. M., *Ann. Allergy*, **11**, 24 (1953)
122. Brown, E. A., *Quart. Rev. Allergy Appl. Immunol.*, **7**, 51 (1953)
123. Mayer, P. S., Masko, M. M., Schutz, P. J., Osterman, F. A., Steen, L. H., and Baker, L. A., *J. Am. Med. Assoc.*, **151**, 351 (1953)
124. Siegel, S., Steinhardt, R. U., and Goerber, R., *J. Allergy*, **24**, 1 (1953)
125. Feinberg, S. M., Feinberg, A. R., and Moran, C. F., *J. Am. Med. Assoc.*, **152**, 114 (1953)
126. Criep, L. H., and De Castillo-Ribeiro, C., *J. Am. Med. Assoc.*, **151**, 1185 (1953)
127. Nilzen, A., *J. Investi Dermatol.*, **18**, 7 (1952)
128. Baer, R. L., and Sulzberger, M. B., *J. Invest. Dermatol.*, **18**, 53 (1952)
129. Baer, R. L., Ferri, F., and Kirman, D., *J. Invest. Dermatol.*, **19**, 217 (1952)
130. Curtis, G. H., *Arch. Dermatol. and Syphilol.*, **65**, 149 (1952)
131. Haxthausen, H., *J. Invest. Dermatol.*, **19**, 293 (1952)
132. Ellis, F. A., and Bundick, W. R., *J. Am. Med. Assoc.*, **150**, 773 (1952)
133. Sidi, E., Malki, G. R., and Longville, R., *Acta Allergol.*, **5**, 292 (1952)
134. Sidi, E., *Semaine hôp. Paris*, **28**, 665, (1952)
135. Rajka, G., *Acta Allergol.*, **5**, 11, (1952)
136. Sidi, E., and Casalis, F., *Semaine hôp. Paris*, **28**, 3282 (1952)
137. Sidi, E., and Longville, R., *Presse méd.*, **61**, 92 (1953)
138. Schulman, L. E., Schalnick, E. H., and McGee, H. A., *Bull. Johns Hopkins Hosp.*, **92**, 196 (1953)
139. Schwartz, M., *Acta Allergol.*, **6**, 134 (1953)
140. Sulzberger, M. B., and Smith, C. C., *J. Am. Med. Assoc.*, **151**, 468 (1953)
141. Goldman, L., O'Hara, H., and Baskett, J., *J. Invest. Dermatol.*, **20**, 272, (1953)
142. Goldman, L., Preston, R., and Rockwell, E., *J. Invest. Dermatol.*, **18**, 89, (1952)
143. Diamond, H. E., *Ann. Allergy*, **11**, 146–56 (1953)
144. Fischer, A. A., *J. Invest. Dermatol.*, **19**, 271 (1952)
145. Tuft, L., and Heck, M. M., *J. Allergy*, **23**, 528 (1952)
146. Abramson, H. A., *J. Am. Med. Assoc.*, **150**, 569 (1952)
147. Abramson, H. A., *Quart. Rev. Allergy Appl. Immunol.*, **7**, 197 (1953)
148. Fagerberg, E., *Acta Allergol.*, **6**, 61–79 (1953)
149. Mansmann, J. A., *Ann. Allergy*, **10**, 583–91 (1952)
150. Lewin, J., *Ann. Allergy*, **11**, 157–69 (1953)
151. Ouer, R. A., *Ann. Allergy*, **11**, 36–41 (1953)
152. Rocwell, G. E., *Ann. Allergy*, **11**, 175–77 (1953)
153. Jenkins, C. M., *Ann. Allergy*, **11**, 96–103 (1953)
154. Wittich, F. W., *Ann. Allergy*, **10**, 625–28 (1952)
155. Rothlin, E., and Cerletti, A., *Intern. Arch. Allergy Appl. Immunol.*, **4**, 191–99 (1953)
156. Parish, F. A., *Ann. Allergy*, **11**, 85–88 (1953)
157. Brushkin, E., *Ann. Allergy*, **11**, 15–23 (1953)
158. Rowe, A. H., *Ann. Allergy*, **10**, 605–14 (1952)

159. Fontana, V. J., *J. Allergy*, **24,** 174 (1953)
160. *Proc. Royal Soc. Med.*, **46,** 253 (1953)
161. *Proc. First Intern. Congr. Allergy* (S. Karger, Basel, Switzerland and New York, N. Y., 1143 pp., 1952)
162. Hensel, F. F., *Clinical Allergy* (C. V. Mosby Co., St. Louis, Mo., 1005 pp., 1953)

NEOPLASTIC DISEASES[1]

MEDICAL CARE IN ADVANCED CANCER

By Alfred Gellhorn

Medical Service, Francis Delafield Hospital, New York, New York

AND

James F. Holland

National Cancer Institute, Bethesda, Maryland

Introduction

There are an estimated 700,000 cancer patients under medical care each year in the United States (1). Annually, 211,000 individuals die from cancer, a total greater than the combined mortality from motor vehicle accidents, homicide, suicide, diabetes, tuberculosis, pneumonia, chronic nephritis, peptic ulcer, and cirrhosis of the liver. These two statistics justify the attention of the medical profession to neoplastic diseases.

Investigation of abnormal and normal growth has continuously been extended from the clinical specialties to most of the basic scientific disciplines. An increasing body of knowledge from the laboratory is now becoming available to the physician and the integration of clinical and fundamental studies affords a reasonable hope for future progress. At present, despite improvements in diagnosis and curative therapy, the majority of patients who develop cancer eventually die from their disease. This review emphasizes certain recent aspects of laboratory and clinical research pertinent to the care of the patient with advanced malignant disease.

Nitrogen Metabolism

It has long been known that the presence of an actively growing malignant tumor is associated with an increased energy production by the host, which may on occasion be conveniently demonstrated by an elevation of basal metabolic rate. Furthermore, Mider and his colleagues (2) have shown that a tumor-bearing rat contains fewer calories than his pair-fed control. This difference in caloric content represents the energy expended during tumor growth. In instances where the mass of tumor is manifestly too small to account for all the increased oxygen consumption, it is clear that alterations have transpired in the host's tissues which require more energy. The exact nature of these alterations is unknown. When dietary calories are inadequate to satisfy the augmented energy requirement, fat is metabolized. Breakdown of protein with deamination of amino acids to provide adequate

[1] The survey of literature pertaining to this review was completed in September, 1953.

substrate for energy production may occur if the caloric deficit be sufficiently great.

The metabolic characteristics of the cancerous individual can best be appreciated if one considers separately the tumor and the host; together they constitute the patient. When both adequate calories and sufficient protein precursors are supplied for the tumor and the host, the host tissues can be maintained approximately in nitrogen equilibrium in short term studies (3). If, however, inadequate calories are available from the diet or from metabolized fat depots, or if insufficient dietary nitrogen is presented to the tumor-bearing individual, the host goes into negative nitrogen balance. The tumor continues to incorporate nitrogenous constituents from the metabolic pool which during dietary deficiency presumably derive in great part from muscle protein. Deamination of amino acids for energy production aggravates the absolute loss of nitrogen to the host. Whether one can measure this as negative nitrogen balance for the patient as a whole, however, by study of the ingesta and excreta, is dependent on the algebraic sum of tumor and host balance. During certain stages of active tumor growth there is incorporation of nitrogen-containing moieties by the tumor and protein sacrifice by the host. In this circumstance, excreted nitrogen may be less than that ingested, and positive balance for the patient is thus recorded (4). If, however, extensive deamination of amino acids to satisfy energy requirements is in progress, the excretion of nitrogen will exceed intake and negative nitrogen balance is measured.

It is not as yet known whether host protein molecules can be incorporated as such, or whether the growing tumor can use only amino acids and peptides (5). That there are serious alterations of host protein metabolism is amply illustrated by the changes in circulating proteins which have been observed. Mider *et al.* have studied the serum albumin concentration in relation to tumor growth and have demonstrated a hypoalbuminemia with more advanced disease (6). In mice with lymphosarcoma, Norberg & Greenberg (7) have shown that C^{14}-labeled glycine attains higher concentrations in the liver protein and the plasma proteins than in normals. These data are compatible with more active protein synthesis in the liver and greater protein transport in the plasma. Together with hypoalbuminemia, such findings suggest that albumin utilization may be more rapid in tumor-bearing than in normal subjects.

Recent experiments indicate that globulin synthesis is not depressed by malignant disease. Balch (8) has studied anamnestic antibody responses to diphtheria toxoid in severely depleted preterminal cancer patients. From his data it can be calculated that in 14 patients with carcinoma the average maximum concentration of antitoxic protein produced was 106 mg. per cent; for three patients with sarcoma and one with myeloma the average was 185 mg. per cent. These figures are to be contrasted to 19 well-nourished normals, whose average antitoxic protein was 92 mg. per cent. The levels did not correlate with the concentrations of total plasma protein nor of serum albumin,

but are consonant with Mider's analyses in which gamma globulin was increased, though not to a level of statistical significance as were fibrinogen, and the alpha one and alpha two globulins (6). Larson, using pneumococcus polysaccharide, observed antibody production comparable to normals in patients with Hodkin's disease, lymphosarcoma, and chronic myelocytic leukemia (9).

Associated with rapid proliferation there is increased protein synthesis by the tumor cells and competition for substrates exists between the host and the neoplasm. LePage *et al.* (10) studied the behavior of 2-C^{14}-glycine in rats with the Flexner-Jobling carcinoma. After a single injection, the total radioactivity in the tumor increased continuously, while that in liver and kidney declined. This phenomenon was independent of exogenous protein intake, proceeding essentially unchanged in fasted rats. Thus, the tumor continued to incorporate amino acids while the host was being depleted of them, a demonstration of the lack of equilibrium between tumor and the general metabolic pool. There is no tumor contribution to the bodily demands during starvation, but rather continuing parasitism. Zamecnik and his co-workers (11), moreover, have shown that the ability of hepatoma to incorporate the C^{14}-label of glucose into amino acids is far greater than that of normal liver. If such an organization of intermediary metabolism selectively to synthesize protein precursors from glycogen precursors is universal, it would be an important aspect of neoplastic protein anabolism.

Mider and his colleagues (12, 13) have analyzed both tumor and carcass in rats bearing carcinomas and lymphomas on diets which are adequate to maintain nutrition in normal rats. There was more nitrogen in the tumor than the total positive nitrogen retention from external sources, and this must therefore have come from the animal carcass. In a study by Begg & Dickinson (14), when rats were force fed during tumor growth, no loss of carcass weight was noted. Stewart & Begg extended this study, however, and in spite of forced feeding noted that carcass weight loss (15) and decrease in the carcass content of nitrogen (16) occurred eventually. If, with adequate nitrogen and adequate calories, destruction of host proteins still ensues, a considerable modification is required in the widely accepted concept that host protein metabolism could be maintained if there were adequate substrate. It is conceivable that some neoplasms may have exaggerated needs for certain nutrients, but no specific deficiencies occasioned in the host thereby have been recognized. Mider has obtained evidence supporting the concept that malignant tumors in rats incorporate substances essential to the host. The anorexia and carcass wasting of tumor-bearing rats was strikingly reversed when lyophilized tumor was given in their diet (17). The possibility exists therefore that progressive cachexia may be incidental to the tumor needs for a particular component of other tissues. Deprivation of the host to satisfy the neoplasm in this requirement would allow the nosologic classification of cachexia in the course of advanced malignant disease as an induced specific deficiency. Another hypothesis advanced to explain cachexia in

cancerous individuals is the elaboration of a toxic factor by the tumor which interferes with normal metabolic processes in the host. Such a factor has not been isolated.

Positive nitrogen balance indicative of tumor anabolism has been repeatedly observed in patients with actively growing cancers (3, 4, 18). Following therapeutic response to nitrogen mustard, in one instance of a patient with lymphosarcoma reported by Fenninger *et al.*, the expected negative nitrogen balance which follows normal tissue destruction did not ensue (19). From a study of simultaneous balance data of other protoplasmic constituents, it was possible to calculate that protein from the destroyed tumor was utilized by the host tissues. No such effect was seen in the same patient when remission was induced with corticotropin, perhaps because of the known effects of the hyperadrenal state in inhibiting anabolism in normal tissues.

The extent of present knowledge of protein metabolism in the host and in the tumor is still manifestly incomplete. The insight into the mechanisms of tumor growth and into the host's response to the presence of cancer that may be gained by further study of protein metabolism justifies continuation of this important approach. The therapeutic application of knowledge already gained is limited. In the course of advanced cancer in man, the nutrition of the host may become a critical factor for survival. Although in animals retardation of tumor growth can be achieved by starvation (20) it seems wiser clinically to forego this theoretical possibility in favor of an attempt to maintain adequate nutrition for the host. Despite major anorexia, caloric and protein intakes which are raised to more nearly normal levels are frequently associated with benefit.

CALCIUM METABOLISM

Interest continues in the problems of bone metastases and calcium metabolism. The frequency of osseous lesions in cancer affords a broad area for study. Destruction of bone by metastatic tumor is associated with mobilization of bone salts, and the measurement of calcium in the excreta provides a convenient index of tumor activity. One gram of bone contains approximately 150 mg. of calcium (21), but it is not certain that a quantitative relation exists between the volume of bone mechanically replaced and the amount of calcium liberated. Partial demineralization adjacent to metastatic loci without actual tumor involvement may occur, in addition to generalized osteoporosis from debility and inadequate nutrition. In the course of osteolysis, however, if the host's normal bone be in calcium equilibrium, one may expect the mobilized calcium to appear in the excreta. Urinary excretion accounts for nearly all, but, to a much lesser degree, enteric excretion of endogenous calcium has also been shown. Utilizing balance techniques, Laszlo (18) has studied many patients with osteolytic metastases from carcinoma of the breast. In postmenopausal patients without exogenous hormone he has demonstrated fluctuation in urinary calcium excretion consistent with intermittent growth and quiescence of the metastases. Pearson has also described

an increase in calcinuria premenstrually in three of six young women (22).

During periods of hypercalcinuria, regardless of the serum calcium level, inadequacy of renal tubular reabsorption of water may occur. Since microscopic examination at autopsy may fail to reveal significant deposition of calcium salts (23), it is likely that this disorder is intimately associated with derangements arising from a high concentration of calcium within the tubular cells. Also, the polyuria may spontaneously subside concomitant with, or after, a return of urinary calcium excretion to normal. This "calcinuric diabetes" is characterized by hyposthenuria, inconstant response to pitressin administration, and variable depression of phenolsulphthalein excretion.

If the calcium mobilized by bone destruction is in excess of that which the kidney can excrete, hypercalcemia occurs. In none of Laszlo's patients was a normal serum calcium concentration maintained when calcinuria became intense; the highest urinary calcium with a normal serum level was 643 mg./day. When the serum calcium was 12 mg. per cent or more, the average urinary excretion was 614 mg./day. In no instance of hypercalcemia was the urinary level less than 350 mg./day (18).

The presence of hypercalcemia constitutes one of the most serious of the electrolyte abnormalities encountered in medicine. Anorexia, nausea, vomiting, constipation, apathy, obtunded mentation, coma, and death may all occur. Early compromise of glomerular function with azotemia and uremic death, at a time when metastatic renal calcification may be unimpressive, suggests that abnormalities are induced in glomeruli or in the renal vasculature by hypercalcemia which are not appreciated by microscopic examination (23, 24). Renal functional abnormalities of some degree are a characteristic concomitant of the hypercalcemic state (25, 26, 27). Azotemia may disappear entirely, however, if the hypercalcemia remits.

The treatment of hypercalcemia is in large measure supportive and expectant. Restoration of fluid and electrolyte losses, which may be occasioned by the anorexia, vomiting, or renal disease, is imperative. Water diuresis, if it can be established without precipitating significant edema, may be of great benefit.

In the hypercalcemic patient with breast cancer who has not had testosterone, administration of this steroid may be associated with striking improvement (26). The precise mechanism is unknown, although it is assumed that because of tumor inhibition by testosterone, rapid osteolysis ceases and hypercalcemia and hypercalcinuria abate. Hypercalcemia which occurs during sex hormone therapy may be attributable to progression of bone destruction by cancer independent of the administered hormone, or to actual stimulation of tumor growth. Inasmuch as differentiation between these two mechanisms is impossible without prolonged and hazardous observation, administration of the drug should be terminated. Discontinuation may be followed by return to normal calcium metabolism or to initiation of a period of distinct bone repair (28).

Attempts to bind the excessive amounts of circulating calcium ions by

chemical substances which have the ability to form complexes with them have been disappointing. Sodium citrate infusions are widely employed, but no controlled studies of their immediate depressing effect on calcium concentration in hypercalcemic patients are available. The compound is rapidly metabolized. It is known that no serum calcium depressions are seen 24 hr. later (26), nor do infusions regularly result in enhanced urinary excretion of calcium (29). A study of the possible applications of sodium ethylene diamine tetra acetic acid (Versene, Sequestrene), a stronger chelating agent, has demonstrated its lack of clinical utility (27). Whereas the serum level can be immediately depressed, even to dangerous levels, return to hypercalcemic concentrations occurs in a very few hours. This is predominantly attributable to mobilization of skeletal calcium rather than dissociation of the complex, for a great proportion of the chelated calcium appears as such in the urine (30). No clinical improvement was seen as a result of the drug.

The incidence of hypercalcemia has not been well studied in relation to all the carcinomas which commonly metastasize to bone. It is generally agreed that the syndrome is most commonly seen in patients who have metastases from carcinoma of the breast, where its spontaneous incidence is about 15 per cent (25). In the course of therapy with testosterone, Kennedy *et al.* observed seven instances of hypercalcemia in 97 patients with bone metastases treated with testosterone (26). Other reports are of this same order of magnitude. Hypercalcemia in the course of diethylstilbestrol therapy is less frequent; this may reflect in part the nature of the disease in the predominantly postmenopausal women treated with this agent. Carcinomas of the kidney, lung, prostate, stomach, and thyroid, and multiple myeloma, malignant melanomas, leiomyosarcoma, and acute leukemia all have been reported to cause sufficient calcium mobilization to precipitate hypercalcemia. The effects of sex steroid hormones on the bone disease in these patients is considerably less impressive than that which obtains in breast cancer (28), although it may be dramatic on occasion.

Laszlo and his associates have extensively employed the technique of calcium infusions and have studied the varying responses observed in patients with osseous metastases (31). After the administration of 446 mg. of calcium to normal subjects in four hours (as 10 per cent calcium gluconate) they were able to recover 302 ± 14 mg. in the urine in 24 hr.; in the patients with osteoblastic metastases 50 ± 14 mg. were found; patients with osteolytic metastases excreted 469 ± 92 mg. The calcium tolerance test faithfully reflected changes in the same patient, when healing or exacerbation was occurring, providing a quantitative index of the avidity of bone for the increased calcium load. This technique may be of considerable aid in studies of calcium metabolism since it correlates well with conclusions obtained from balance data.

ANEMIA

An important manifestation of the effect of a malignant tumor on its host is anemia. Although blood loss secondary to tumor ulceration is significant

in the pathogenesis of anemia in many instances of carcinoma of the gastro-intestinal and genitourinary tracts, it has increasingly been recognized that this fails to explain the development of anemia in the majority of patients with disseminated neoplastic disease. An inadequate rate of erythrocyte production or an accelerated rate of red cell destruction are other mechanisms which may lead to anemia. Two factors might possibly be operative in depressing erythropoiesis: replacement of normal bone marrow elements by tumor cells, or faulty synthesis of hemoglobin, associated either with disturbances of cell protein metabolism or with insufficient precursors due to malnutrition. The infrequency of ante- or post-mortem evidences of extensive myelophthisis (32) and the indication of accelerated red cell production obtained from studies of radio-iron incorporation into hemoglobin (33 to 36) suggest that these factors are not of major importance in the pathogenesis of a large proportion of the anemias of cancer.

The failure of blood loss or erythropoietic depression to explain the development of anemia in the majority of patients with widespread neoplasms has emphasized the possibility of increased red cell destruction. Although instances of overt hemolysis have been reported in patients with leukemia, lymphoma, and carcinomatosis (37), these are rare. Brown *et al.* (38) and Ross (39), employing Ashby's technique of differential agglutination (40, 41), recently demonstrated that the life span of transfused normal red cells was only 30 to 50 per cent of the expected value in patients with leukemia or malignant lymphoma. Of particular interest were the associated observations made by these investigators that reticulocyte counts, the serum bilirubin, osmotic fragility, fecal urobilinogen excretion, and the Coomb's test for autoantibodies all failed to indicate the presence of an active hemolytic process. In a series of patients with metastatic carcinoma, Hyman (42) has shown a marked increase in the rate of destruction of transfused erythrocytes. These studies indicate that a major factor in the pathogenesis of anemia in neoplastic disease is a discrepancy in the relative rates of red cell production and destruction such that, though erythropoiesis may be increased, red cell loss from the circulation is even greater.

The mechanism for the accelerated destruction of red cells in cancer has not been determined. It is certainly not solely attributable to a structural or chemical defect in the patient's own erythrocyte because normal red cells are destroyed rapidly when transfused into the cancerous subject. In addition, Ranney (43) has failed to find any electrophoretic abnormalities in the hemoglobin of cancer patients even when there is marked marrow involvement by tumor cells. It is possible that the *in vitro* observations of Gross (44, 45) on the presence of a hemolytic factor in extracts of tumor tissues may be pertinent to this problem.

A somewhat greater understanding of the mechanism of anemia in neoplastic disease has not led to major therapeutic applications. In autoimmune hemolytic anemias, cortisone and ACTH (adrenocorticotropin) have proved of some value. There have been well documented cases of hemolytic anemia

in leukemia which have benefited from cortisone (46). The pragmatic observation has been made that the hemoglobin of patients with advanced Hodgkin's disease and lymphosarcoma can be better maintained by transfusions if cortisone is given. This is not to be considered a substitute for definitive therapy with x-ray or nitrogen mustard. The effect of cortisone on the increased rate of destruction of transfused red cells in patients with epithelial tumors is under study (47) but available evidence indicates less efficacy of this regimen than in patients with lymphomas and leukemias.

RADIOTHERAPY

Radiotherapy is important not only in the primary attack on certain tumors where the objective is total eradication of disease, but also in the management of inoperable or recurrent carcinomas. It is a fact that all cells, regardless of their origin, can be destroyed by radiotherapy. The unsuccessful radiotherapeutic assault on most cancers is explained by the local and systemic toxicity to normal tissues which must be balanced against the cancericidal effect of the radiation so that the host is not destroyed together with his tumor. It follows from this that relatively superficial and well localized neoplasms such as those involving the skin, the oral cavity, the larynx, and the cervix (which also are, in the main, radiosensitive) can with regularity be effectively treated by radiotherapy. As the extent of the tumor increases or as the volume of normal tissue between the tumor and the source of radiant energy becomes large, a safe dose of radiation may not be tumoricidal. Clinical experience has provided a working concept of the range of tolerance doses for the various normal tissues of the body. For example, it is recognized that the central nervous system and muscle are less susceptible to damage by radiation than the bone marrow, gonads, and intestine and furthermore that infection, anemia, hypoproteinemia, and impaired circulation all increase the radiation hazard to a tissue (48). In recent years there have been developments in radiotherapy which have added to the significance of this knowledge.

In cooperation with physicists, therapeutic radiologists have determined by experimentation on appropriate models the tissue dose at various depths delivered by a variety of sources of radiant energy. From these data, isodose curves have been established from which the therapist can calculate in a given patient the precise dose of radiant energy which will be absorbed by normal and tumor tissue under a given set of conditions. With this knowledge the radiotherapist may be able to increase the tumor dose of radiation by crossfiring the neoplasm through multiple portals or by rotating the patient in the x-ray beam and thereby accomplish the desired objective with greater safety (49).

Another development in radiation therapy is the clinical use of supervoltage equipment in the form of mega volt x-ray generators, betatrons, and multicurie cobalt 60 or radium teletherapy units (50 to 55). It is to be

emphasized that the enthusiastic and unrealistic claims made for supervolt-age therapy in the lay press do not reflect the opinions expressed by radio-therapists. Although the public has been led to believe that supervoltage implies supereffect, it should be recognized by the medical profession that there is no evidence to suggest that there are qualitative differences between the effects of radiations produced by conventional radiotherapy units and supervoltage machines. A significant quantitative difference has been achieved, however, with the new equipment. The increased energy source of radiation increases the quality of penetration, decreases the scatter of radiation within the body, and lowers the absorption by the skin. These at-tributes permit the delivery of depth tumor doses which could not be given by the usual equipment without hazard to intervening or surrounding nor-mal tissues. Although many hundreds of patients have been treated with supervoltage machines, sufficient time has not elapsed to evaluate the long term results. Particular attention and interest will be focused on the results of therapy of deep-seated neoplasms such as bronchogenic and esophageal carcinoma.

Radioisotopes have aided tremendously in advancing biological knowl-edge, but their value in therapeutics is limited. The use of radioiodine in thyroid carcinoma may provide impressive palliation in those patients with a functional tumor (56). Unfortunately, only about 12 per cent of thyroid cancers incorporate significant amounts of radioiodine and efforts to induce function in nonfunctional tumors by thyroid ablation and the administra-tion of anti-thyroid drugs are far from satisfactory. Rawson has reported that about 5 per cent of nonfunctional tumors can be induced to take up therapeutically effective amounts of radioiodine (57, 58). Seidlin (59) and Frantz and her associates (60, 61) have had little success in inducing iodine avidity in their patients with this regimen or with thyrotropic hormone.

The use of radioactive colloidal gold in the control of pleural and peri-toneal effusions associated with malignant neoplastic disease is sometimes of value (62 to 68). This isotope of gold (Au^{198}) has several properties which are advantageous for intracavitary therapy. Of the radiation absorbed at the surface, 90 to 95 per cent is attributable to a moderately energetic β-particle which exerts its action within a range of a few millimeters. This permits the application of high doses of radiation to the surface of serous cavities without exposing the subjacent tissues. The half life of Au^{198} is 2.7 days which is sufficiently long to permit shipment and preparation for use without undue difficulty and sufficiently short so that the length of exposure of tissues to radiation is not excessive. The colloidal gold is pharmacodynamically inert so that gold intoxication presents no problem and the absorption of the part-icles through lymphatics or their distant transportation by histiocytes is minimal.

Consideration of the use of intracavitary radioactive colloidal gold therapy is indicated when intractable pleural or peritoneal effusions exist re-

sulting from tumor metastases on the serous surfaces. The accumulated experience of a number of clinics suggest that in about 50 per cent of the patients there is a significant decrease in the rate of reaccumulation of pleural effusions or ascites (69). The brevity of improvement in many instances is attributable to death of the patient from progression of his tumor. Where this does not occur, effective reduction of fluid accumulation may be measurable in months. It must be recognized that the radiogold, at best, is affecting only the most superficial layers of cells and cannot, therefore, be expected to modify the fundamental course of the disease. This does not vitiate the usefulness of the isotope in relieving a distressing complication of many disseminated neoplasms.

There is still no unanimity of opinion on optimal radioactive gold dosage. The intraperitoneal instillation of 100 to 150 mc. and the use of 50 to 75 mc. intrapleurally are widely advocated. Radiation sickness may follow the instillation of the isotope, but this is usually of brief duration. There are precautions which must be exercised in the preparation and administration of the radioactive material for protection of personnel (70).

In the selection of cases it is wise to establish the frequency with which taps are necessary before resorting to intracavitary radiogold. Occasionally one is happily surprised to find that following a single thoracentesis or paracentesis the effusion does not recur or is formed sufficiently slowly so that more definitive measures are not necessary. In the presence of loculated fluid, intracavitary radiation is of limited value particularly when this occurs within the peritoneal cavity where the hazard is great either from perforation of the intestine by the trocar or from necrosis of a viscus resulting from intensive irradiation.

In the past year, two patients with pericardial effusions secondary to metastatic bronchogenic carcinoma had 35 mc. of radiogold instilled into the pericardial sac with equivocal therapeutic benefit but without local radiation damage (71).

Brief mention should be made of developments in the prophylaxis and therapy of radiation injury. A variety of substances have been reported to have some protective action against x-rays in animals, but none has been of clinical usefulness (72, 73, 74). Recently, Bacq et al. (75) and others have reported that β-mercaptoethylamine, (cysteinamine, Becaptan) is a potent drug for the prevention of death in mice given lethal doses of x-ray and also is therapeutically valuable in radiation sickness in man. Although the objective evaluation of therapy in the radiation sickness syndrome is notoriously difficult, the results obtained in experimental studies in animals justify further evaluation clinically. The mechanism of action of the compound is thought to depend upon its reaction with free radicals liberated in the body by ionizing radiation.

Potentially of far greater importance than those compounds which act only in prophylaxis of radiation injury is the growing experimental evidence for a humoral factor produced by certain living cells which is capable of in-

stituting recovery of tissues after radiation injury has been sustained. The observations of Jacobson (76) on the reduction of mortality of mice exposed to a single lethal dose of total body x-radiation by shielding the exteriorized spleen initiated a number of provocative studies. At the present time it has been shown that the intraperitoneal implantations of homologous or heterologous splenic tissue, of embryo suspensions, or of bone marrow suspensions are therapeutically effective in reducing radiation injury (77). All attempts thus far to extract the factor or factors from these tissues have been unsuccessful. It has been established that these unirradiated intact cells bring about an early recovery of the blood-forming tissue of irradiated animals. Whether they also lead to the functional reconstitution of other cells has not been established. Although no clinical applications of these experiments have been made to problems of radiation injury or radiation therapy, the potentialities are obviously great.

CHEMOTHERAPY

It is a reasonable estimate that surgery and radiotherapy cure only 25 per cent of all patients with malignant tumors. Major improvement in results by these methods is not anticipated. These considerations together with the increasing frequency of cancer, reveal the magnitude of the problem left to other medical specialties. Two possible approaches to its solution can be formulated: the discovery and application of drugs which on systemic administration destroy tumor cells without possessing forbidding toxicity, and prevention of a proportion of cancers by recognition and elimination of carcinogenic environmental factors.

In recent years there have been a number of reviews on cancer chemotherapy (78 to 85) so that recapitulation of the laboratory background and current clinical status of all useful drugs is not warranted here. In the past year, however, there have been several developments in this field which merit attention. To provide a framework for the discussion, Table I groups

TABLE I

MECHANISM OF ACTION OF CANCER CHEMOTHERAPEUTIC DRUGS

Change in Host with Deleterious Effects on Cancer Cell	Change in Response of Host to Cancer	Direct Effect on Cancer Cell	
Estrogens in prostatic and male breast cancer	Androgens and estrogens in cancer of female breast; ACTH and Cortisone in lymphomas, multiple myeloma and acute leukemia of adults	Nitrogen mustard Triethylene Melamine Urethane Folic acid antagonists 6-Mercaptopurine Myleran	in lymphomas and leukemias
		Cortisone and ACTH in acute leukemia of children	

the drugs which are of value in the therapy of certain human neoplastic diseases according to their major mechanism of action.

No new drugs have been introduced which can be characterized as altering the environment of the cancer cell unfavorably, analogous to the action of estrogens in carcinoma of the prostate. The ending of a remission induced by castration and estrogen administration in prostatic cancer has been attributed by some to the secretion of androgenic hormones by the adrenal cortex. On the basis of this hypothesis, and the availability of cortisone for postoperative maintenance, Huggins (86) has performed bilateral total adrenalectomies in patients with refractory carcinoma of the prostate. Although preliminary reports were encouraging, longer periods of observation disclosed that the predominant effect of adrenalectomy in prostatic cancer was temporary alleviation of pain without significant modification of the course of the disease. Accordingly, the procedure has largely been discontinued.

Since the course of cancer of the female breast may be altered by sex hormones, bilateral adrenalectomy was also performed in such patients with refractory, disseminated lesions (87). Of twelve postmenopausal or castrated patients, nine had subjective and objective improvement following removal of bóth adrenals (88). The period of follow-up is too brief to determine the duration of the remissions. Other clinics have had less favorable results in patients with breast cancer. West *et al.* (89) reported objective and subjective improvement in two of five patients for four months. Hudson (90) has observed no objective regressions and significant symptomatic benefit in only one of fifteen women. The effect of adrenalectomy on a variety of other human cancers has been studied. These include carcinomas of the esophagus, stomach, lung, kidney, and colon; malignant melanoma; acute leukemia and Hodgkin's disease. None has shown significant improvement. The results of hypophysectomy have recently been reported in twelve patients with malignant tumors. Conclusive appraisal is not yet possible, but preliminary reports do not seem encouraging (91).

To classify the effect of androgens and estrogens in cancer of the female breast as modification of host response to the tumor is a personal choice of the authors and not shared by all workers in the field. It is recognized that sex hormone therapy in women with disseminated carcinoma of the breast can occasionally produce impressive cytologic changes with objective tumor regression (92). In the vast majority of patients, however, androgen therapy in younger women, or estrogen therapy in the older postmenopausal patients, is only associated with subjective relief of bone pain, an increase in appetite, and a greater sense of well-being. Objectively, during this period of symptomatic improvement, progression of the tumor in soft tissue or bone can frequently be demonstrated. These effects can be explained in part by the protein anabolic action of the hormones, their ability to stimulate the deposition of osteoid, and by the psychic response of rejuvenation which often accompanies the administration of these drugs. Undesirable side reactions

occur with both hormones. Testosterone propionate, the most commonly used androgen, produces signs and symptoms of virilization which occasionally may be sufficiently pronounced to necessitate discontinuation of the drug. Both testosterone and stilbestrol, the most frequently used estrogen, can cause hypercalcemia, and edema because of salt and water retention.

Substitutes for testosterone propionate have been sought which would have equal or greater therapeutic efficacy in breast cancer with less androgenicity. During the past year, it has been suggested that the derivative dihydrotestosterone (Neodrol, stanolone) attains these objectives (93, 94). In a clinical evaluation conducted on 26 patients by the authors and Herrmann and his associates (95), however, this drug was not found to possess any advantages over testosterone propionate. Methyl testosterone has activity comparable to that of testosterone propionate and is effective when given by mouth (96). This advantage is in part counterbalanced by the occurrence of jaundice attributable to bile stasis with plugging of the canaliculi in the central zones of the liver lobules (97). Although this has not been reported to be a fatal toxic reaction nor yet a very common one, it is a serious complication because the jaundice is slow to resolve. ACTH and cortisone have no apparent effect on it other than to stimulate appetite (98).

The compounds characterized in Table I as having a direct effect on cancer cells are useful in the clinical management of the malignant lymphomas and the leukemias. In addition, therapeutic applications of nitrogen mustard and triethylene melamine have been made in certain carcinomas. The intrapleural injection of nitrogen mustard to control pleural effusion in patients with bronchogenic carcinoma has been reported (99). This procedure is also effective in pleural effusions attributable to other malignant diseases. The technique is simple. The effusion is almost completely removed and through the same needle nitrogen mustard in a small volume of saline solution is injected. The usual nausea, vomiting, and bone marrow depression seen after intravenous administration may occur depending upon the amount of the drug absorbed transpleurally. The therapy leads to obliteration of the pleural space attributable either to a direct effect on the malignant cells or to irritation of the pleural surfaces. We have studied fifteen patients who had required frequent thoracenteses for recurrent symptomatic effusions. Using the same criteria to determine when thoracentesis was needed again after intrapleural mustard, a significant benefit was obtained in seven. In three, equivocal improvement was achieved, whereas in five patients we could appreciate no decrease in the frequency with which thoracentesis was necessary. In a number of instances, repeated instillations of small amounts of nitrogen mustard were made when decrease in rate of fluid accumulation was not apparent. In this series of patients the usual injection of nitrogen mustard was 5 to 10 mg.; some patients received 0.3 mg./kg. body weight without undue toxicity. It is hoped that the larger dose will be effective in a greater proportion of future patients. The results of this small series are comparable to those

achieved with intrapleural radioactive colloidal gold (100). The availability, low cost, and ease of administration of the nitrogen mustard are considerable advantages.

Rundles & Barton (101) have reported that triethylene melamine, an orally active congener of nitrogen mustard, exhibits therapeutic potency in metastatic cystadenocarcinoma of the ovary. Others have confirmed these results, and the drug should be considered when radiotherapy and surgery are no longer of benefit.

The uses of urethane and folic acid antagonist drugs have been extensibly described in earlier reports. Noteworthy change in their status has not occurred. Studies of the mechanisms of action of these and other cytotoxic drugs have uniformly indicated an interference with some phase of nucleic acid metabolism. This has stimulated the synthesis of cancer chemotherapeutic agents with preconceived structure-activity relationships.

A clinically useful compound which has been reported during the past year is 6-mercaptopurine (Purinethol) (102). This drug, developed by Hitchings & Elion, is an analog of hypoxanthine and of adenine (103, 104, 105). It inhibits the growth of a variety of microorganisms (106), several mouse leukemias and many transplantable tumors in mice and rats (107, 108). Clinically, Burchenal and his associates (109) have demonstrated that the drug produces remissions in acute leukemia in children with about the same regularity as the folic acid analogs. As with these latter drugs, the disease inevitably becomes refractory to 6-mercaptopurine. It is of considerable theoretical interest as well as practical importance that acute leukemia, resistant to the folic acid antagonists, may still respond favorably upon the administration of 6-mercaptopurine. This suggests that the mechanism of action of the purine analog and the folic acid antagonist is different. Elion & Hitchings (110), using microbiological methods, have offered evidence which indicates that 6-mercaptopurine inhibits the conversion of adenine to guanine, thereby interfering with a pathway in nucleic acid synthesis.

6-Mercaptopurine is therapeutically active upon oral administration in doses of 1 to 3 mg./kg. body weight daily. The toxic reactions are primarily attributable to bone marrow depression with pancytopenia. In addition to its usefulness in acute leukemia of children (and to a very much lesser extent in acute leukemia of adults), 6-mercaptopurine appears to be of some value in the treatment of reticulum cell lymphosarcoma (111), and in the more acute terminal phases of chronic myelocytic leukemia (109). Other types of malignant lymphoma, the chronic leukemias, and a variety of epithelial tumors have failed to respond.

Another drug which has recently been evaluated in the chemotherapy of cancer is 1, 4-dimethanesulfonyloxybutane (Myleran) (112, 113). This compound contains bifunctional chemically reactive groups. It was synthesized by Timmis on the basis of cytological studies with nitrogen mustard. Administration of the latter drug leads to imperfect division of chromosomes

during mitosis presumably as a result of cross-linkage of chemical constituents of the chromosome with the two chemically reactive groups in the mustard molecule. It was anticipated that Myleran would behave in a similar manner.

In clinical trails Galton and Haddow found that Myleran was effective in the therapy of chronic myelocytic leukemia, producing a fall in the peripheral leucocyte count, a return of the differential toward normal, and a rise in hemoglobin (114). It is active upon oral administration and produces remissions in chronic myelocytic leukemia comparable to splenic irradiation, urethane, or triethylene melamine. Other laboratory and clinical observations have provided evidence that Myleran is ineffective against other neoplasms including carcinomas of the breast, lung, stomach, and colon; reticulum cell lymphosarcoma; and malignant melanoma (115).

Myleran and 6-mercaptopurine represent drugs which have been developed on a rational basis. The paramount importance of nucleic acids in the biochemical reactions of the cell indicates that interference with the synthesis or function of these complex molecules can reasonably be expected to result in cellular injury or death. The differences in nucleic acid metabolism between normal and tumor cells found thus far have been quantitative rather than qualitative so that, as would be anticipated, toxicity to normal tissues accompanies the chemotherapeutic effect on malignant cells. In addition, it has been demonstrated in clinical cancer chemotherapy, particularly of acute leukemia, that the malignant cells eventually become refractory to an initially effective antitumor drug. The mechanism of this drug resistance has been studied by Burchenal and Law in mouse leukemia. These investigators independently have shown that the phenomenon is attributable to selection of refractory mutant cells by destruction of susceptible ones, so that ultimately the tumor population is composed predominantly of the resistant elements (116, 117, 118). This sequence of events is analogous to the development of antibiotic resistant microorganisms (119). The lack of absolute tumor specificity of antitumor drugs and the phenomenon of drug resistance constitute major limitations to effective cancer chemotherapy. At the present time combinations of drugs which will either sequentially block cellular metabolic reactions or will interfere simultaneously with multiple cellular functions are being investigated (120, 121). Such an approach offers promise of overcoming, at least in part, both of the limitations mentioned, and available experimental findings are encouraging. Clinical application of combination cancer chemotherapy has not as yet been extensively attempted.

In spite of the beginnings of the development of antitumor drugs on a rational basis, there is little doubt that the empirical screening of compounds for cancer chemotherapy must also continue. The correlative evidence of biological or biochemical comparability between transplantable animal tumours and human neoplastic disease is tenuous. For this reason it is impossible to predict that results of chemotherapy on tumors in experimental an-

imals will have relevance when the drugs are tried in human cancer patients. This has suggested the need for a re-evaluation of screening methodology in a search for other biological systems in addition to transplantable tumors in mice, rats, and rabbits.

The clinical evaluation of drugs in the treatment of leukemias and lymphomas has proceeded rapidly and reliably. In these diseases there are many objective criteria such as rapid fluctuation in lymph node masses, fever, and peripheral blood counts which facilitate the testing of a potential therapeutic agent. In the statistically more important group of human neoplastic diseases, the epithelial cancers, the chronicity of disease, the wide variations in natural history, the inaccessibility of tumor masses for accurate mensuration, and the unreliability of evaluations based on symptomatic improvement alone constitute serious obstacles to satisfactory assay of the effects of a candidate compound. This emphasizes the need for more sensitive objective criteria to be used in the evaluation of human anticancer drugs.

PAIN

The evaluation of spontaneous pain and its control is difficult. The subjective nature of pain, the lack of objective criteria for assessing the psychic response to it, and the frequent amelioration by diversion, illustrate some of the factors complicating its measurement. That the patient with pain does not have a lowered sensory threshold, however, is demonstrated by the study of Kennard (122) in which she found that the pain threshold in 24 patients with chronically painful diseases was entirely similar to that of a control group. Several approaches to the control of pain in incurable cancer are employed. None is wholly satisfactory, and irreversible procedures to induce pain relief merit the most cautious forethought.

Palliative operations have become firmly established in the management of the cancer patient. Frequently there are considerations other than pain alone which prompt surgical procedures not designed for cure of cancer. The restoration to more normal physiology, if it can be accomplished, and relief from distressing symptoms thoroughly justifies this approach. Gastrectomy, cholecystecto-jejunostomy, and bowel resection are examples of operations which can be performed properly without intention of cure. The needs of the patient for relief and a reasonable basis for thinking that such improvement can be achieved determine the indications for a palliative operation.

Radiotherapeutic procedures may provide major improvement in bone pain from osteolytic metastases, irrespective of the type of neoplasm. Although calcification of bony lesions does occur, pain relief may be dramatic and persistent without apparent change in the roentgenographic appearance. When soft tissue lesions are painful, irradiation may also diminish pain. We have seen gratifying response in several patients with painful hepatic metastases subjected to radiotherapy.

When patient care must be directed primarily toward the relief of pain, rather than at modification of the painful lesion, several alternatives present themselves. Wherever possible, neurosurgical procedures should be planned primarily in accordance with the patient's prognosis. A reasonable estimate of the duration of pain relief must be correlated with the expected survival. In this regard the injudicious use of addicting drugs is to be deplored, for in the addicted state, pain relief is usually less efficient, and narcotic dependence is a significant disability. Where operative risk or expected survival does not permit extensive surgical procedures, analgesic nerve blocks for regional pain may be of considerable value. Bonica (123) has been a major exponent of alcohol block, and in his hands relief was obtained in 64 per cent of 137 selected patients with pain from cancer. He has also revived interest in the subarachnoid injection of absolute alcohol, which by positioning the patient, can be reasonably well localized to bathe the posterior nerve roots from the painful area (124).

Surgical interruption of the spinothalamic tracts should be considered in certain instances. Intractable pain in an upper extremity is usually well controlled by a combination of unilateral cordotomy at C 1 and section of the posterior nerve roots of C 2 through 5. Bilateral section of the spinothalamic tracts is used to alleviate pain below the nipple line. When the pain is above this however, the hazard of a cordotomy is greatly increased by the respiratory and sphincter problems which follow deeper section of the cervical spinal cord. Cordotomy achieves satisfactory pain relief in two-thirds of well selected cases. Narcotic addiction is not affected when pain is abolished by cordotomy, and this may compromise the appraisal and value of the operative result. Because the mentation of the patient is not modified, cordotomy should be employed wherever the anatomic distribution of pain permits. It must be remembered that further metastatic disease may appear above the level of the cordotomy and require further pain relief, or that lesions of no concern to the patient because of other particularly painful areas may command more attention and be the cause of new complaint after the original pain is relieved.

Prefrontal lobotomy is the most destructive, but in many ways the most successful, of the neurosurgical procedures for the relief of pain. Not only can it modify the appreciation of pain as an unpleasant experience, but it may entirely relieve anxiety associated with a chronic debilitating disease. The disability of intellectual deficit is frequently less than that obtundation associated with suffering and heavy narcotic dosage and is usually outweighed by a gratifying cessation of pain. Bilateral prefrontal lobotomy need not be so extensive for pain relief as the procedure employed in the psychoses. Grant (125) cites collected data indicating that unilateral prefrontal lobotomy is successful in slightly more than half of patients, whereas the bilateral procedure achieves good results in three-fourths. The choice of operation will

depend on the neurosurgeon; the greater efficacy of bilateral lobotomy in spite of its detriments recommends it as the ultimate procedure in pain control.

In spite of therapies designed to eliminate the causes of pain, and surgical efforts to interrupt the nervous pathways carrying pain, the vast number of patients remains who are best managed clinically by narcotic medication. The indication for a pain-relieving drug is pain, and there is no justification for insistence on standardized regimens when the responses to pain are so varied. The weaker analgesics are profitably employed first, but if pain is not relieved, no reluctance to initiate narcotics is defensible. An endeavor to forestall parenteral medication as long as possible is worthwhile, and in this regard, meperidine orally or morphine orally or sublingually may be used with good response. A particularly helpful regimen for ambulatory or home care employs methadone orally at eight or twelve hour intervals for basal pain relief supplemented by sublingual morphine when the need arises. The development of N-allylnormorphine (nalorphine, Nalline) should be of value in the prevention of fatal narcosis if that crisis arises. This structural analogue of morphine has been shown to be an antagonist for morphine, codeine, dihydromorphinone (Dilaudid), metopon, methadone, meperidine (Demerol) and methorphinan (Dromoran) (126, 127, 128).

PSYCHOLOGICAL ASPECTS

The extensive publicity concerning cancer is, in part, an attempt to inform and encourage the laity and the medical profession to act more promptly and more wisely when signs and symptoms of neoplastic disease appear. Since earlier diagnosis and appropriate surgical and radiation therapy are the chief methods currently available for reducing cancer mortality and morbidity, the effort would seem to be well-founded. That such publicity may not be wholly effective, however, is indicated by a study of Robbins, MacDonald & Pack (129) on the delay in diagnosis and treatment in physicians who themselves had cancer. In a group of these patients with "superficial tumors" where the symptoms and signs should have been obvious, there were 66 per cent who did not consult another physician within three months, whereas in comparison only 45 per cent of lay people delayed this long. In other tumor classifications the physician-patient delay was equally appalling and did not reflect earlier diagnosis nor therapy as one might have expected from an informed group. If this be a true reflection of behavior in a physician when confronted with the suspicion that he may have cancer there would appear to be other factors besides information alone which modify the conduct of any patient who suspects he has malignant disease. Numerous studies have indicated that a characteristic emotional attitude, rather than an indifference toward cancer, keeps the patient from early care. Finesinger and his colleagues (130) observed that there is a psychologic defect in the processing of

information readily apparent to the patient which results in the suppression and denial of its existence. There is an attempt "to hold his world together by not looking at evidence that will change it." Abrams & Finesinger (131) in another study of 60 selected patients found that a sense of guilt was strikingly prominent. This, together with feelings of inadequacy and inferiority for harboring cancer led to delay in seeking aid.

The emotional stresses during the course of cancer do not derive entirely from the fear of the disease with its implications of death. The major altera-tions in body anatomy and function which are often the result of radical therapy may lead to significant psychological disturbances. Sutherland *et al.* (132) have admirably begun a semiquantitative appraisal of the impact of cancer surgery upon patients. As one might expect, the stress of colostomy was better tolerated emotionally in those patients who preoperatively were well-adjusted individuals than in those whose personality integration and family life were mediocre or insecure before operation. The results reported, which reflect systematic analysis rather than impression-gathering, are ar-resting indeed. The disruption of normal life routines to center attention on the colostomy was frequently excessive. Bowel function became a fetish, ritualistic behavior was common, and fear of embarrassment and disgrace by poor colostomy control was often all-consuming. The problems of personal-ity adjustment in these apparently cured patients cogently illustrate an as-pect of cancer treatment which merits attention.

In a discussion of psychological aspects of cancer the question of whether to inform the patient about his diagnosis should be considered. No broad background of factual information is available to provide guidance on this issue and therefore the conclusions necessarily will be based on clinical ex-perience and personal interpretation of the role a physician should play in the care of his patient.

The problem may be divided into two general situations: the individual with potentially curable disease, and the incurable patient. If there is rea-sonable prospect of cure by surgery or radiotherapy, it is justifiable to tell a patient the diagnosis if this is essential to gain his cooperation for pro-longed or mutilating treatment. In our opinion, however, such a patient should not be told that he has cancer unless the necessitating circumstance exists. We take this position because, even when presumably curative pro-cedures are carried out, success is not assured. We believe that it is wiser for the attending physician alone to carry the burden of anticipating and search-ing for evidences of recurrent or metastatic disease than to share this respon-sibility with the patient. Certainly a responsible relative of the patient should be advised of the prognosis.

In our experience the necessity for telling a patient with disseminated cancer his actual diagnosis arises very rarely and we strongly deprecate vol-unteering this information. It must be borne in mind that the fear of cancer

is not unreasonable; confirmation of this fear seems needlessly self-right-eous. Understanding discussion with the patient should certainly be encour-aged, and reassurance should be given. The physician can mollify the true status to a great extent by judicious omissions or modifications. We have found that in a hospital for neoplastic diseases, where patient care is intensive and emotional support thereby enhanced, spontaneous interrogation by pa-tients about diagnosis and prognosis is rare. As a corollary, overt expectation of certain death, with the despondency which so frequently accompanies it, is uncommonly encountered.

LITERATURE CITED

1. Dorn, H. F., and Cutler, S. J. (Personal communication, September, 1953)
2. Mider, G. B., Fenninger, L. D., Haven, F. L., and Morton, J. J., *Cancer Research*, **11**, 731 (1951)
3. Pearson, O. H., and Eliel, L. P., *Recent Progr. Hormone Research*, **6**, 373 (1951)
4. Waterhouse, C., Fenninger, L. D., and Keutmann, E. H., *Cancer*, **4**, 500 (1951)
5. Christensen, H. N., and Rafn, M. L., *Cancer Research*, **12**, 495 (1952)
6. Mider, G. B., Alling, E. L., and Morton, J. J., *Cancer*, **3**, 56 (1950)
7. Norberg, E., and Greenberg, D. M., *Cancer*, **4**, 383 (1951)
8. Balch, H. H., *J. Immunol.*, **64**, 397 (1950)
9. Larson, D. L., and Tomlinson, L. J., *J. Clin. Invest.*, **32**, 317 (1953)
10. LePage, G. A., Potter, V. R., Busch, H., Heidelberger, C., and Hurlbert, R. B., *Cancer Research*, **12**, 153 (1952)
11. Zamecnik, P. C., Loftfield, R. B., Stephenson, M. L., and Steele, J. M., *Cancer Research*, **11**, 592 (1951)
12. Mider, G. B., Tesluk, H., and Morton, J. J., *Acta Unio. Intern. contra Cancrum*, **6**, 409 (1948)
13. Sherman, C. D., Jr., Morton, J. J., and Mider, G. B., *Cancer Research*, **10**, 374 (1950)
14. Begg, R. W., and Dickinson, T. E., *Cancer Research*, **11**, 409 (1951)
15. Stewart, A. G., and Begg, R. W., *Cancer Research*, **13**, 556 (1953)
16. Stewart, A. G., and Begg, R. W., *Cancer Research*, **13**, 560 (1953)
17. Mider, G. B. (Personal communication, August, 1953)
18. Laszlo, D., Schulman, C. A., Bellin, J., Gottesman, E. D., and Schilling, A., *J. Am. Med. Assoc.*, **148**, 1027 (1952)
19. Fenninger, L. D., Waterhouse, C., and Keutmann, E. H., *Cancer*, **6**, 930 (1953)
20. Tannenbaum, A., and Silverstone, H., *Cancer Research*, **13**, 532 (1953)
21. Pearson, O. H., and West, C. D., *Proc. Am. Assoc. Cancer Research*, **1**, 42 (1953)
22. Pearson, O. H., West, C. D., and Treves, N. E., *J. Clin. Invest.*, **32**, 594 (1953)
23. Sproul, E. E. (Personal communication, September, 1953)
24. Escher, D., *Recent Progr. Hormone Research*, **6**, 415 (1951)
25. Swyer, A. J., Berger, J. S., Gordon, H. M., and Laszlo, D., *Am. J. Med.* **8**, 724 (1950)
26. Kennedy, B. J., Tibbetts, D. M., Nathanson, I. T., and Aub, J. C., *Cancer Research*, **13**, 445 (1953)
27. Holland, J. F., Danielson, E., and Sahagian-Edwards, A., *Proc. Soc. Exptl. Biol. Med.*, **84**, 359 (1953)
28. Laszlo, D., Schilling, D., Bellin, J., Gottesman, E. D., and Schulman, C. A., *J. Am. Med. Assoc.*, **148**, 1502 (1952)
29. Shorr, E., Almy, T. P., Sloan, M. H., Taussky, H., and Toscani, V., *Science*, **96**, 587 (1942)
30. Spencer, H., Vankinscott, V., Lewin, I., and Laszlo, D., *J. Clin. Invest.*, **31**, 1023 (1952)
31. Schilling, A., and Laszlo, D., *Proc. Soc. Exptl. Biol. Med.*, **78**, 286 (1951)
32. Shen, S. C., and Homburger, F., *J. Lab. Clin. Med.*, **37**, 182 (1951)
33. Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M., and Lawrence, J. H., *J. Clin. Invest.*, **29**, 1041 (1950)
34. Cartwright, G. E., and Wintrobe, M. M., *Advances in Internal Med.*, **5**, 165 (1952)

35. Wasserman, L. R., Raskoff, I. A., Leavitt, D., Mayer, J., and Port, S., *J. Clin. Invest.*, **31**, 32 (1952)
36. Hyman, G. H. (Unpublished observations)
37. Stats, D., Rosenthal, N., and Wasserman, L. R., *Am. J. Clin. Pathol.*, **17**, 585 (1947)
38. Brown, G. M., Elliott, S. M., and Young, W. A., *J. Clin. Invest.*, **30**, 130 (1951)
39. Ross, J. F., *J. Clin. Invest.*, **30**, 668 (1951)
40. Ashby, W., *J. Exptl. Med.*, **29**, 267 (1919)
41. Dacie, J. V., and Mollison, P. L., *Lancet*, **I**, 550 (1943)
42. Hyman, G. H., *Blood* (In press)
43. Ranney, H. (Personal communication, September, 1953)
44. Gross, L., *Proc. Soc. Exptl. Biol. Med.*, **65**, 292 (1947)
45. Gross, L., *J. Immunol.*, **59**, 173 (1948)
46. Dameshek, W., Saunders, R. H., and Zannos, L., *Bull. New Engl. Med. Center*, **12**, 11 (1950)
47. Gellhorn, A., and Hyman, G. H. (Unpublished observations)
48. Lenz, M., *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **67**, 428 (1952)
49. Jacox, H. W., and Collins, V. P., *The 1952 Year Book of Radiology*, 269–71 (The Year Book Publishers Inc., Chicago, Ill., 416 pp. 1952)
50. Cantril, S. T., and Buschke, F., *Radiology*, **53**, 313 (1949)
51. Hare, H. F., Lippincott, S. W., Jr., Sawyer, D., Trump, J. G., Webster, E. W., Wright, K. A., Evans, W. W., and Granke, R. C., *Radiology*, **57**, 157 (1951)
52. Murphy, W. T., and Reinhard, M. A., *Radiology*, **55**, 477 (1950)
53. Harvey, R. A., Haas, L. L., and Laughlin, J. S., *Radiology*, **58**, 23 (1952)
54. Editorial, *Radiology*, **58**, 113 (1952)
55. Smith, I. H., *J. Can. Assoc. Radiologists*, **3**, 16 (1952)
56. Seidlin, S. M., Rossman, I., Oshry, E., and Siegel, E., *J. Clin. Endocrinol.*, **9**, 1122 (1949)
57. Rawson, R. W., Rall, J. E., and Peacock, W., *J. Clin. Endocrinol.*, **11**, 1128 (1951)
58. Rall, J. E., Miller, W. W., Foster, C. G., Peacock, W. C., and Rawson, R. L., *J. Clin. Endocrinol.*, **11**, 1273 (1951)
59. Seidlin, S. M., *Med. Clin. N. Amer.* **36**, 1 (1952)
60. Frantz, V. K., Larsen, W. G., and Jaretzki, A., *J. Clin. Endocrinol.*, **10**, 1084 (1950)
61. Frantz, V. K. (Personal communication, June, 1953)
62. Hahn, P. F., and Carothers, E. L., *Nucleonics*, **6**, 54 (1950)
63. Kent, E. M., and Moses, D., *J. Thoracic Surg.* **22**, 503 (1951)
64. Rose, R. G., Osborne, M. P., and Stevens, W. B., *New Engl. J. Med.*, **247**, 663 (1952)
65. Stapleton, J. E., and Wingo, W. J., *Nucleonics*, **10**, 63 (1952)
66. King, E. R., Spicer, D. W., Dowda, F. W., Binder, M. A., and Noel, W. E., *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **68**, 413 (1952)
67. Andrews, G. A., Root, S. W., Kerman, H. D., and Bigelow, R. R., *Ann. Surg.*, **137**, 375 (1953)
68. Andrews, G. A., Root, S. W., and Knisely, R. M., *Cancer*, **6**, 294 (1953)
69. *Administration and uses of radioactive colloidal gold 198*, Abbott Laboratories, Dept. Radioactive Pharm., (June, 1953)
70. Ter-Pogossian, M., and Sherman, A. I., *Nucleonics*, **10**, 23 (1952)
71. Gellhorn, A. (Unpublished observations)

72. Patt, H. M., Smith, D. E., Tyree, E. B., and Straube, R. L., *Proc. Soc. Exptl. Biol. Med.*, **73**, 18 (1950)
73. Boyland, E., and Gallico, E., *Brit. J. Cancer*, **6**, 160 (1952)
74. Cole, L. J., Bond, V. P., and Fishler, M. C., *Science*, **115**, 644 (1952)
75. Bacq, Z. M., Deschamps, G., Fisher, P., Herve, A., LeBihan, H., Lecomte, J., Pirotte, M., and Rayet, P., *Science*, **117**, 633 (1953)
76. Jacobson, L. O., *Cancer Research*, **12**, 315 (1952)
77. Lorenz, E., *J. Natl. Cancer Inst.*, **12**, 197 (1951)
78. Karnofsky, D. A., *New Engl. J. Med.*, **239**, 226, 260, 299 (1948)
79. Karnofsky, D. A., *Stanford Med. Bull.*, **6**, 257 (1948)
80. Gellhorn, A., and Jones, L. O., *Am. J. Med.*, **6**, 188 (1949)
81. Karnofsky, D. A., Burchenal, J. H., and Escher, G. C., *Med. Clin. N. Amer.*, **34**, 1 (1950)
82. Karnofsky, D. A., and Burchenal, J. H., *Am. J. Med.*, **8**, 767 (1950)
83. Gellhorn, A., *Cancer Research*, **13**, 205 (1953)
84. Gellhorn, A., *Am. J. Urol.* (In press)
85. Gellhorn, A., *The Physiopathology of Cancer*, 854-920 (Paul B. Hoeber, Inc., New York, N. Y., 1031 pp., 1953)
86. Huggins, C. and Bergenstal, D. M., *Cancer Research*, **12**, 134 (1952)
87. Huggins, C. and Dao, T. L., *Ann. Surg.*, **136**, 595 (1952)
88. Dao, T. L., *Science*, **118**, 21 (1953)
89. West, C. D., Hollander, V. P., Whitmore, W. F., Jr., Randall, H. T., and Pearson, O. H., *Cancer*, **5**, 1009 (1952)
90. Hudson, P. (Personal communication, September, 1953)
91. Luft, R., and Olivecrona, H., *J. Neurosurg.*, **10**, 301 (1953)
92. Emerson, W. J., Kennedy, B. J., Graham, J. N., and Nathanson, I. T., *Cancer*, **6**, 641 (1953)
93. Farrow, H., Escher, G. C., Sved, D. W., Urban, J. E., Robbins, G., Breed, C., and Treves, N. E., *Proc. Am. Assoc. Cancer Research*, **1**, 10 (1953)
94. Escher, G. C., Farrow, J. H., Sved, D. W., Robbins, G., Woodard, H. Q., and Treves, N. E., *Proc. Am. Federation Clin. Research* (In press)
95. Gellhorn, A., Holland, J., Herrmann, J., Moss, J., and Smelin, A., *J. Am. Med. Assoc.* (In press)
96. Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **146**, 471 (1951)
97. Werner, S. C., Hanger, F. M., and Kritzler, R. A., *Am. J. Med.*, **8**, 325 (1950)
98. Gellhorn, A., and Holland, J. (Unpublished observations)
99. Karnofsky, D. A., Abelman, W. H., Craver, L. F., and Burchenal, J. H., *Cancer*, **1**, 634 (1948)
100. Holland, J., and Gellhorn, A. (Unpublished results)
101. Rundles, R. W., and Barton, W. B., *Blood*, **7**, 483 (1952)
102. Burchenal, J. H., Karnofsky, D. A., Murphy, M. L., Ellison, D. A., and Rhoads, C. P., *Proc. Am. Assoc. Cancer Research*, **1**, 7 (1953)
103. Hitchings, G. H., Elion, G. B., Falco, E. A., Russell, P. B., and VanderWerff, H., *Ann. N. Y. Acad. Sci.*, **52**, 1318 (1950)
104. Elion, G. B., Hitchings, G. H., and VanderWerff, H., *J. Biol. Chem.*, **192**, 505 (1951)
105. Elion, G. B., Burgi, E., and Hitchings, G. H., *J. Am. Chem. Soc.*, **74**, 411 (1952)
106. Elion, G. B., Singer, S., Hitchings, G. H., Balis, M. E., and Brown, G. B., *J. Biol. Chem.*, **202**, 647 (1953)

107. Clarke, D. A., Philips, F. S., Sternberg, S. S., Stock, C. C., Elion, G. B., and Hitchings, G. H., *Cancer Research*, **13**, 593 (1953)
108. Sugiura, K., *Proc. Am. Assoc. Cancer Research*, **1**, 55 (1953)
109. Burchenal, J. H., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W., and Rhoads, C. P., *Blood*, **8**, 965 (1953)
110. Elion, G. B., Singer, S., and Hitchings, G. H., *J. Biol. Chem.*, **204**, 35 (1953)
111. Hyman, G. H., Osserman, E., and Gellhorn, A. (Unpublished observations)
112. Timmis, G. M., *Ann. Rept. Brit. Empire Cancer Campaign*, **28**, 56 (1950)
113. Haddow, A., and Timmis, G. M., *Lancet*, **I**, 207 (1953)
114. Galton, D. A. G., *Lancet*, **I**, 208 (1953)
115. Gellhorn, A., Holland, J., Hirschberg, E., and Kells, A. M., *Proc. Am. Assoc. Cancer Research*, **1**, 18 (1953)
116. Burchenal, J. H., Robinson, E., Johnston, S. F., and Kushida, M. H., *Science*, **111**, 116 (1950)
117. Law, L. W., and Boyle, P. J., *Proc. Soc. Exptl. Biol. Med.*, **74**, 599 (1950)
118. Law, L. W., *Nature*, **169**, 628 (1952)
119. Newcombe, H. B., *Nature*, **164**, 150 (1949)
120. Skipper, H., *Proc. Am. Assoc. Cancer Research*, **1**, 51 (1953)
121. Shapiro, D. M., and Gellhorn, A., *Cancer Research*, **11**, 35 (1951)
122. Kennard, M. A., *J. Clin. Invest.*, **31**, 245 (1952)
123. Bonica, J. J., *J. Am. Med. Assoc.*, **150**, 1581 (1952)
124. Bonica, J. J., *J. Michigan State Med. Soc.*, **52**, 284 (1953)
125. Grant, F. C., *Chicago Med. Soc. Bull.*, **55**, 45 (1952)
126. Eckenhoff, J. E., Elder, J. D., Jr., and King, B. D., *Am. J. Med. Sci.*, **223**, 191 (1952)
127. Fraser, H. F., Wikler, A., Eisenman, A. J., and Isbell, H., *J. Am. Med. Assoc.*, **148**, 1205 (1952)
128. Domino, E. F., Pelikan, E. W., and Traut, E. F., *J. Am. Med. Assoc.*, **153**, 26 (1953)
129. Robbins, G. F., Macdonald, M. C., and Pack, G. T., *Cancer*, **6**, 624 (1953)
130. Shands, H. C., Finesinger, J., Cobb, S., and Abrams, R. D., *Cancer*, **4**, 1159 (1951)
131. Abrams, R. D., and Finesinger, J., *Cancer*, **6**, 474 (1953)
132. Sutherland, A. M., Orbach, C. E., Dyk, R., and Bard, M., *Cancer*, **5**, 857 (1952)

DISEASES OF THE NERVOUS SYSTEM[1]

METABOLIC ASPECTS OF SOME NEUROLOGICAL AND MUSCULAR DISORDERS

By Frank H. Tyler and Marvin D. Armstrong

Laboratory for the Study of Hereditary and Metabolic Disorders and the Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah

Through the years, considerable evidence has been accumulated which suggests that metabolic changes may be the underlying causes of certain muscular, neurologic, and mental diseases. The feeling has come to exist among clinicians as well as biochemists that the pathologic processes in these disorders involve alterations of fundamental chemical reactions. Research in this direction has been greatly accelerated in recent years, and in several disorders a considerable amount of information has been gathered concerning the pathologic process. It is the purpose of this review to consider recent application of metabolic studies in a few selected disorders. These range from phenylketonuria, in which a well-defined inherited metabolic anomaly invariably is associated with mental deficiency, to schizophrenia, for which the question of whether there is an underlying metabolic derangement responsible for the varied manifestations of the psychosis remains a vigorously debated point. A review such as this raises many more questions than it can possibly settle, but demonstrates the theoretical considerations which are the basis for many of the clinical and biochemical investigations now underway.

The genetic nature of many of these disorders is a fundamental characteristic. It is now a widely accepted view that the genes control the formation of enzymes which are necessary for metabolic processes, and that when a gene is either missing or abnormal certain reactions are distorted. Where specific genetic metabolic anomalies have been established in such organisms as *Neurospora crassa* and *E. coli* they appear to affect only a single enzyme or metabolic transformation in any given mutation. A discussion of the attempts to trace some human diseases back to an abnormality of a single enzymatic process is the basic aim of this review.

Schizophrenia

Earlier studies of schizophrenia have been summarized in reviews by Hoskins (1), Bellak (2), and Gillies (3). The past two or three years have witnessed the appearance of many contributions derived from applications of modern techniques of biochemistry, physiology, and clinical medicine to the problem of the etiology of the psychoses. At the present time there appear to be several biochemical and physiological differences between schizophrenic and normal individuals. It has not been shown whether the psychic difficulty

[1] The survey of literature pertaining to this review was completed in July, 1953.

107. Clarke, D. A., Philips, F. S., Sternberg, S. S., Stock, C. C., Elion, G. B., and Hitchings, G. H., *Cancer Research*, **13**, 593 (1953)
108. Sugiura, K., *Proc. Am. Assoc. Cancer Research*, **1**, 55 (1953)
109. Burchenal, J. H., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W., and Rhoads, C. P., *Blood*, **8**, 965 (1953)
110. Elion, G. B., Singer, S., and Hitchings, G. H., *J. Biol. Chem.*, **204**, 35 (1953)
111. Hyman, G. H., Osserman, E., and Gellhorn, A. (Unpublished observations)
112. Timmis, G. M., *Ann. Rept. Brit. Empire Cancer Campaign*, **28**, 56 (1950)
113. Haddow, A., and Timmis, G. M., *Lancet*, **I**, 207 (1953)
114. Galton, D. A. G., *Lancet*, **I**, 208 (1953)
115. Gellhorn, A., Holland, J., Hirschberg, E., and Kells, A. M., *Proc. Am. Assoc. Cancer Research*, **1**, 18 (1953)
116. Burchenal, J. H., Robinson, E., Johnston, S. F., and Kushida, M. H., *Science*, **111**, 116 (1950)
117. Law, L. W., and Boyle, P. J., *Proc. Soc. Exptl. Biol. Med.*, **74**, 599 (1950)
118. Law, L. W., *Nature*, **169**, 628 (1952)
119. Newcombe, H. B., *Nature*, **164**, 150 (1949)
120. Skipper, H., *Proc. Am. Assoc. Cancer Research*, **1**, 51 (1953)
121. Shapiro, D. M., and Gellhorn, A., *Cancer Research*, **11**, 35 (1951)
122. Kennard, M. A., *J. Clin. Invest.*, **31**, 245 (1952)
123. Bonica, J. J., *J. Am. Med. Assoc.*, **150**, 1581 (1952)
124. Bonica, J. J., *J. Michigan State Med. Soc.*, **52**, 284 (1953)
125. Grant, F. C., *Chicago Med. Soc. Bull.*, **55**, 45 (1952)
126. Eckenhoff, J. E., Elder, J. D., Jr., and King, B. D., *Am. J. Med. Sci.*, **223**, 191 (1952)
127. Fraser, H. F., Wikler, A., Eisenman, A. J., and Isbell, H., *J. Am. Med. Assoc.*, **148**, 1205 (1952)
128. Domino, E. F., Pelikan, E. W., and Traut, E. F., *J. Am. Med. Assoc.*, **153**, 26 (1953)
129. Robbins, G. F., Macdonald, M. C., and Pack, G. T., *Cancer*, **6**, 624 (1953)
130. Shands, H. C., Finesinger, J., Cobb, S., and Abrams, R. D., *Cancer*, **4**, 1159 (1951)
131. Abrams, R. D., and Finesinger, J., *Cancer*, **6**, 474 (1953)
132. Sutherland, A. M., Orbach, C. E., Dyk, R., and Bard, M., *Cancer*, **5**, 857 (1952)

DISEASES OF THE NERVOUS SYSTEM[1]

METABOLIC ASPECTS OF SOME NEUROLOGICAL AND MUSCULAR DISORDERS

By Frank H. Tyler and Marvin D. Armstrong

Laboratory for the Study of Hereditary and Metabolic Disorders and the Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah

Through the years, considerable evidence has been accumulated which suggests that metabolic changes may be the underlying causes of certain muscular, neurologic, and mental diseases. The feeling has come to exist among clinicians as well as biochemists that the pathologic processes in these disorders involve alterations of fundamental chemical reactions. Research in this direction has been greatly accelerated in recent years, and in several disorders a considerable amount of information has been gathered concerning the pathologic process. It is the purpose of this review to consider recent application of metabolic studies in a few selected disorders. These range from phenylketonuria, in which a well-defined inherited metabolic anomaly invariably is associated with mental deficiency, to schizophrenia, for which the question of whether there is an underlying metabolic derangement responsible for the varied manifestations of the psychosis remains a vigorously debated point. A review such as this raises many more questions than it can possibly settle, but demonstrates the theoretical considerations which are the basis for many of the clinical and biochemical investigations now underway.

The genetic nature of many of these disorders is a fundamental characteristic. It is now a widely accepted view that the genes control the formation of enzymes which are necessary for metabolic processes, and that when a gene is either missing or abnormal certain reactions are distorted. Where specific genetic metabolic anomalies have been established in such organisms as *Neurospora crassa* and *E. coli* they appear to affect only a single enzyme or metabolic transformation in any given mutation. A discussion of the attempts to trace some human diseases back to an abnormality of a single enzymatic process is the basic aim of this review.

SCHIZOPHRENIA

Earlier studies of schizophrenia have been summarized in reviews by Hoskins (1), Bellak (2), and Gillies (3). The past two or three years have witnessed the appearance of many contributions derived from applications of modern techniques of biochemistry, physiology, and clinical medicine to the problem of the etiology of the psychoses. At the present time there appear to be several biochemical and physiological differences between schizophrenic and normal individuals. It has not been shown whether the psychic difficulty

[1] The survey of literature pertaining to this review was completed in July, 1953.

results in a biochemical defect, or vice versa. Although our knowledge of the characteristics of normal mental functioning is meager, it seems more reasonable to assume that an abnormality in a biochemical or physiological process might lead to abnormal functioning of the brain than that a psychic difficulty might lead to the observed changes in biochemical processes.

The study of certain drugs which cause mental and pharmacological reactions which bear a striking resemblance to some of the findings observed in schizophrenia has aroused considerable interest. Work of earlier investigators is cited in recent publications by Rinkel *et al.* (4), Hoch, Cattell & Pennes (5), and Osmond & Smythies (6). Osmond and Smythies have proposed an appealing theory of the etiology of schizophrenia and, in addition, have presented a readable discussion of many of the problems posed by the illness. They cite the symptoms of mescaline poisoning, in which behavior is produced in normals not unlike that observed in schizophrenic patients, and suggest that the primary fault in schizophrenia may lie in the production of an abnormal mescaline-like or "M" substance by the adrenal glands. According to their view, the inherited latent fault (7) resides in the adrenals, which under the stimulus of continual stress produce a toxic substance, perhaps related chemically to the normal hormones. Its effects lead to mental symptoms which produce an additional stress, i.e., a feeling of terror or confusion in the victim and this, in turn, leads to further adrenal dysfunction. Osmond and Smythies admit that mescaline itself is not sufficiently toxic at low levels to be the causative agent, hence they suggest a mescaline-like or "M" substance. No evidence of the presence of such a substance of adrenal or other origin has beeen found in psychotic patients.

Many investigators have been impressed by the extremely minute quantity of lysergic acid diethylamide which, likewise, is capable of producing dramatic mental symptoms not unlike those of schizophrenia. Blickenstörfer (8) has suggested that a related derivative with a similar activity may be produced as a result of abnormal metabolism of proteins or amino acids and may thus be an etiologic factor in the psychoses.

Results of investigations of the correlation between abnormalities of endocrine function and the schizophrenic state have continued to appear in profusion. Two types of evidence have been reported which bear on this problem. The first and most definitive is the observation that in patients with several types of endocrine abnormalities an unusually high incidence of psychoses is found. The fact is now well documented in Cushing's syndrome (9, 10) and myxedema (11, 12) and apparently is also true in hyperparathyroidism (13) and certain other typical endocrine dysfunctions (14). In addition, a considerable literature has accumulated to suggest that psychoses are precipitated if not caused by therapeutic hyperadrenocorticism induced with adrenocorticotropic hormone (ACTH) or cortisone used in the treatment of rheumatoid arthritis, disseminated lupus, and other disorders (15). The relation of the premorbid personality and the primary disease to the response has been the subject of much speculation, the consensus of opinion being that

the psychotic reaction is related in type and severity to the basic personality of the patient and that the disease and its therapy operate only as a sort of trigger mechanism. It should be emphasized, however, that these conclusions concerning basic personality were made in retrospect and cannot be considered to have been adequately controlled.

The second type of evidence has been that purporting to show an abnormality of endocrine function in all psychotic patients and has a much less solid basis. Attention has been focused recently on the status of the adrenals in schizophrenia and other psychoses. The paradox of hyperadrenocortical states precipitating psychoses as compared with apparent deficient adrenal function in other psychotic patients without primary endocrine disease remains unexplained; this has been noted by Altschule (16). However, considerable literature has appeared which suggests that the adrenal cortex of such patients is deficient in its response to exogenous ACTH (17, 18) or to stresses such as insulin hypoglycemia or electroshock (19 to 22). These studies used such metabolic effects as eosinophil levels and uric acid or 17-ketosteroid excretion for the assay of adrenal activity; these effects, however, are not specific. In addition, a more recent and better controlled study by Dickes et al. (23) has failed to confirm certain of these observations, although studies of 17-ketosteroid excretion seem to show, at least statistically, a decreased rate of excretion of these substances (24, 25, 26). Bliss and his collaborators (27) have recently reinvestigated this problem with new methods for the estimation of 17-hydroxycorticosteroids in plasma and urine; these substances have been shown to be the principal adrenal secretions in man (28). Schizophrenic patients have shown the same control values, diurnal variation, response to ACTH and to violent stresses as those observed in normal individuals (27). Thus, the data concerning adrenocortical function and reactivity to stress are conflicting and the reasons for the discrepancies are not clear at present.

One possibility which has not been adequately evaluated in many of the reports claiming to show impaired adrenal function is the debilitated state which frequently develops in patients who have been hospitalized in psychiatric institutions for long periods. Decreased 17-ketosteroid excretion is a practically universal phenomenon in debilitated patients regardless of the cause of the debility. Thus, the observed data may be completely nonspecific insofar as the psychosis is concerned. Although there seems to be real reason to doubt that deficient adrenal secretion of normal hormones is etiologically related to schizophrenia, it should be emphasized that this does not change the possibility that some abnormal metabolic process in the adrenals or elsewhere is the basis of the disorder.

Many schizophrenic patients manifest a prolonged glucose tolerance curve and considerable resistance to the action of insulin (1). Subsequent studies by Simon & Garvey (29) have confirmed the reduced glucose tolerance but also have furnished similar data in other psychoses, including senility, so that its specificity for schizophrenia is dubious. Essentially all of these

studies have been done with Exton-Rose type glucose tolerance tests which are notoriously difficult to interpret when values are obtained in the range just above normal averages. Older studies of insulin sensitivity were performed with subcutaneous insulin, which is sometimes quite variable in its action. A study with the standard intravenous insulin tolerance test in schizophrenics receiving insulin shock therapy has failed to confirm the claim that insulin resistance occurs (30).

A report that the urine of schizophrenic patients contains considerable amounts of a hyperglycemic factor (31) may have some connection with these earlier observations. The presence of this material has been confirmed (32), and the hyperglycemic substance has been subjected to preliminary purification; it appears to be either protein in nature or some substance strongly bound to protein (33). The significance of the excretion of this material by schizophrenic patients remains to be established, as has been noted by Mayer-Gross (34).

Following an earlier report by Quastel & Wales (35) of an imparied ability of schizophrenics to synthesize hippuric acid after ingestion of benzoic acid, many investigators have used this test in studying schizophrenia. The original finding of a decreased excretion of hippuric acid related somehow to the degree of clinical involvement appears to have been confirmed, but the significance of the finding remains unclear. Ordinarily it is presumed that this test indicates some type of liver dysfunction. In this regard, a relation between the thymol turbidity test and the Quick test in schizophrenia has been reported by Nandi (36), but other more specific evidence of hepatic dysfunction has not been forthcoming. It is interesting to note that Fischer, Georgi & Weber (37) have reported that pharmacological doses of mescaline or lysergic acid diethylamide cause a decreased excretion of hippuric acid following the administraction of sodium benzoate. The effect may be a specific biochemical one related in some fashion to the psychosis rather than an evidence of general impairment of liver function.

Bischoff (38) and Brenner & Breier (39) have reported an elevated serum level of copper in schizophrenia, but Munch-Petersen (40) has been unable to find any significant difference between patients and normals (40). In view of the elevated tissue copper levels observed in Wilson's disease, it would be interesting if this finding in schizophrenia were confirmed.

The evidence that has accumulated which suggests that glutamic acid may possess a key position in the metabolism of nervous tissue makes interesting a report by Munkvad (41) concerning a significant difference between the relative amounts of glutamic acid and glutamine in the plasma of normals and schizophrenic patients. Normally about 2.29 mg. per 100 ml. of free glutamic acid and 7.68 mg. per 100 ml. of glutamine is found in the plasma. In active schizophrenia the level of glutamic acid is lowered (in one case as low as 0.31 mg. per 100 ml.) while the level of glutamine is correspondingly elevated to as high as 9.68 mg. per 100 ml. The significance of this observation remains to be determined.

Schizophrenic patients have been shown by a group using chromato-

graphic techniques to excrete a variety of unknown metabolites not found in the urine of normal individuals (42). It is to be expected that many of these substances will be identified in the near future, and may give clues to abnormalities of metabolism which might be of importance in the understanding of the disease. Because it has been proposed so frequently that a toxic substance may be responsible for the onset of schizophrenia, the importance of this type or work cannot be overestimated. Newly developed and convenient methods for separation of small amounts of substances from complex mixtures by ion exchange, adsorption and partition chromatography, and countercurrent distribution used in conjunction with the classical methods of organic chemistry and sensitive methods for detecting unknown materials on paper chromatograms render very hopeful the prospect that abnormal constituents which may be present in material from patients may soon be isolated and identified.

Hoskins (1) comments that "the schizophrenic patient labors under a considerable tendency to circulatory sluggishness." This opinion, which was supported by a considerable amount of experimental evidence, has received additional support so far as the circulation in the extremities is concerned. Altschule & Sulzbach (43) reviewed previous work on the sluggish circulation of the hands and feet of schizophrenic patients, and studied the effect of carbon doxide on their acrocyanosis. They found that carbon dioxide could alter the condition and concluded that there is no structural abnormality of the vasomotor system in schizophrenia. Henschel, Brožek & Keys (44) compared the indirect vasodilatation of the skin of the hands of normals and patients, and found a delayed but normal response in the patients. They also concluded that there is no evidence of structural abnormality of the peripheral vessels in schizophrenia, but that there is either an exceptionally high and persistent state of tonus in the skin vessels or an abnormally high temperature threshold in the hypothalamus. Doust et al. (45, 46) carried out oximetric studies in patients with various types of neurological and mental disorders and found evidence of a chronic peripheral anoxemia in schizophrenic patients. These observations on what is perhaps an exaggerated vasoconstriction of the peripheral capillaries may be correlated with the greater tolerance to histamine therapy of patients discussed by Sackler et al. (47). That these findings may be closely related to the mental deterioration is indicated by experiments reported by Altschule et al. (48, 49) who found that changes in the mental condition of patients were produced by factors affecting blood flow.

Thus, many studies of metabolic changes in schizophrenia have appeared. The accumulated evidence is suggestive that a metabolic derangement does underlie the disease process and it may be hoped that the discovery of its nature will be forthcoming in the near future.

PHENYLKETONURIA (PHENYLPYRUVIC OLIGOPHRENIA)

Reviews of earlier work on phenylketonuria have appeared (50, 51); material covered in them will not be repeated here.

A recent paper by Jervis (52) contains experimental evidence which confirms his previous suggestion that the inherited metabolic block is a failure of the enzyme system in the liver of affected individuals to carry out the oxidation of phenylalanine to tyrosine in a normal manner. Whether this block occurs because an enzyme or cofactor is missing or because of the presence of an inhibitory substance has not yet been determined. It has been found by Udenfriend & Bessman (53) that, although phenylketonurics have lost most of their ability to oxidize phenylalanine to tyrosine, they are still able to form a slight but significant amount of tyrosine from phenylalanine. It is not possible at present to assess the significance of this finding.

The great interest of biochemists and clinicians in studying phenylketonuria lies in the fact that in this condition an inherited defect in a relatively well-defined metabolic reaction of an amino acid, normally carried out in the liver, is associated with a profound mental defect. Some insight might be gained into normal brain metabolism if it were possible to establish the exact mechanism by which the defect develops. It is intriguing to speculate that the cause of a variety of other mental ailments might lie in other metabolic abnormalities working through the same final mechanism. Little progress has been made up to the present time, however, in the attempts to determine the mechanism by which the mental defect occurs.

A majority of the affected individuals are at the idiot level and at least 90 per cent have been found to have intelligence quotients below 50 per cent (50), but great variation in the degree of intellectual impairment is known to occur. Despite the fact that the early extensive surveys of this condition revealed no cases with intelligence even approaching dull normal, several patients have recently been observed with a lesser degree of mental deterioration. Thus, Cowie (54) reported a seven-year-old male phenylketonuric of dull normal intelligence. Jervis (55) has observed a six-year-old phenylketonuric with an I.Q. of 86; Yannet (56) reports a fourteen-year old phenylketonuric of I.Q. 90; Fields (57) found an eighteen-month-old child who did not show a profound retardation of mental and motor development and Armstrong & Tyler (58) studied a thirteen-month-old phenylketonuric who showed little, if any, retardation. It is indeed remarkable that, in a condition where patients have such a wide spread in mental ability, the known metabolic defect has been shown to be so uniform, as indicated by the work of Borek et al. (59) and Jervis (60). To date, it has not been possible to connect the degree of the mental defect with a significant variation in any objective clinical or biochemical measurement.

Few hypotheses have been advanced to account for the mental defect which accompanies the known biochemical defect. Rimington (61) suggested that the presence of large amounts of phenylalanine, itself, in the blood and tissues of the affected individuals might be toxic. This toxicity might be occasioned by an interference by phenylalanine with the absorption of other amino acids into nerve cells, which could cause an intracellular amino acid deficiency and a consequent abnormality in normal protein synthesis. Also, the presence of large amounts of phenylalanine inside cells might interrupt

normal metabolism. For instance, it is conceivable that phenylalanine might interfere with glutamate metabolism by inhibiting glutamine formation; this would lead to the accumulation of higher than normal levels of ammonia, which is known to be highly toxic to nerve cells. In connection with the suggestion of Rimington, it should be noted that in normal individuals there is considerable constancy in the plasma levels of total amino acids and in the relative amounts of the individual amino acids. Phenylketonuria represents a unique situation in that the level of one amino acid frequently becomes as high as the combined total for all of the amino acids in normals.

Recently, Woolf et al. (62, 63) demonstrated the presence of considerable amounts of phenylacetylglutamine, the conjugation product of phenylacetic acid, in the urine of phenlketonurics, and proposed the interesting hypothesis that the mental defect might occur as a result of long continued phenylacetic acid intoxication. Phenylacetic acid had earlier been shown to be detrimental to the central nervous system when administered at high levels (64).

A considerable advance in research on the mental defect in phenylketonuria would result if it could be determined whether the defect occurs because of the presence of toxic substances, formed either directly from phenylalanine or from other metabolities as a consequence of the presence of high levels of phenylalanine, or whether it is attributable to the lack of an enzyme, cofactor, or intermediate which is missing in phenylketonuria. The obvious experiment which might decide between these possibilities is to feed phenylketonurics a diet deficient in phenylalanine to see whether approximately normal levels of phenylalanine can be induced in them, and, if so, to see whether any objective change in mental ability is produced. Armstrong & Tyler (58) have maintained two four-year-old phenylketonuric children on synthetic diets in which the protein component was supplied by an amino acid mixture; phenylalanine was omitted from the mixture for an initial depletion period of two weeks, during which time their blood phenylalanine decreased to approximately normal levels and urinary phenylpyruvic acid excretion ceased. Phenylalanine was then incorporated into their diets at a level low enough that no increase in blood phenylalanine occurred; they were maintained under observation in this condition for a period of three months. Some definite changes in the behavior of the children were observed, but no sustained or dramatic progression in their mental abilities was noted, nor did a significant relapse occur when phenylalanine-containing diets were given with a resulting recurrence of the biochemical anomalies. A similar experiment has been carried out by Bickel et al. (65), with more encouraging results. They used an acid hydrolysate of casein from which phenylalanine and tyrosine had been removed by adsorption on charcoal; tyrosine and tryptophan were returned to the mixture before it was used. Their patient was a profoundly affected two and one-half-year-old child. The child showed dramatic improvement when the experimental diet was given and an equally dramatic relapse occurred when phenylalanine was returned to the diet. This divergence in results in the two laboratories calls for further experimentation.

It is possible that the age of patients or degree of involvement may play a role in the results to be expected from feeding them diets deficient in phenylalanine.

Another facet of the study of phenylketonuria which remains relatively unexplored is whether the mental defect exists from birth at a constant level, or whether deterioration occurs with age. There seems to be no doubt that many cases are profoundly affected from a very early age. Jervis (66) has considered this point in an early paper on the defect—

> The intellectual defect showed unquestionably the characteristic of failure of development and not that of disintegration of developed mentality. In the whole series mental defect was obvious during the first year or, at most, by the second year. In only two cases did there seem to be normal development of mentality during the first year, followed by progressive deterioration, but in both these cases the available data were too uncertain and unreliable to warrant any conclusion. It seems, however, that in a certain number of cases slow mental deterioration of an already low mentality may occur in successive years, as was evidenced in three cases in which successive psychometric examinations were available. In ten other cases successive examinations failed to reveal any changes of mental level.

Unfortunately, up to the present time only a few observations of very young phenylketonurics have been reported. It may be significant in this respect that most of the early studies on phenylketonuria were made on older patients and that the cases of phenylketonurics with higher than usual intellect, cited in this review, are all children. The rarity and nature of the defect is such that affected infants usually will be discovered only when they are siblings of older diagnosed phenylketonurics. A consideration of the progression in six children (58) indicated the possibility that four of them might have progressed almost normally until the age of 4 to 12 months and then regressed; certainly, at the time they were observed (4 to 12 yrs.) they performed less well than interviews with parents indicated they had done at an early age. In the other two cases, the defect was almost certainly present at about the same level from a very early age.

Another development of possibly major significance lies in reports of unidentified metabolites which occur in the urine of phenylketonurics. It may be that biochemical anomalies other than the failure of normal phenylalanine oxidation exist in these patients and that one of these is the cause of the mental deficiency. Thus, Berry & Woolf (67) have reported an unidentified keto acid, Dobriner, Rhoads & Lieberman isolated a new nitrogen containing compound (68), Cowie (51) comments upon an unknown nitrogen-containing "substance A", and Armstrong (69) has observed ether-soluble acidic materials which do not occur in significant amounts in the urine of normal individuals, some phenolic in nature and some which give color reactions characteristic of indole derivatives. Because of the lack of correlation of the amounts of the substances so far positively identified in phenylketonuric urine with the degree of mental defect, the nature of the unknown metabolities is of great interest.

Further discussion of many plausible theories which could be advanced

to explain the mental defect and its relation to the metabolic block in the metabolism of phenylalanine would be fruitless at this time in the absence of additional experimental data. Rapid developments in the study of phenyl-ketonuria may be expected in the near future.

PROGRESSIVE MUSCULAR DYSTROPHY

There are a number of genetically and clinically independent disorders classified as progressive muscular dystrophies. The most common forms are the childhood, facioscapulohumeral, and myotonic types (70). Childhood dystrophy is a rapidly progressive disorder having a sex-linked recessive inheritance (71). The facioscapulohumeral type is a more benign disorder having a later onset and a variable progression; it is transmitted by simple dominant inheritance (72). Myotonia dystrophica is an extremely variable disorder with a dominant inheritance; it is frequently associated with a number of other anomalies in addition to the muscular atrophy. The latter appears to be similar to that observed in the other types of hereditary dystrophy. Mental deficiency is present in about ten per cent of the patients with myotonic dystrophy. In addition, in middle and late life a majority of them develop abnormal behavior patterns which are not found in patients with other types of muscular disability.

The problem of the mechanism of the muscular wasting in these disorders has absorbed the attention of many clinicians and biochemists. A majority of the older reports implicated endocrine dysfunction as the fundamental abnormality responsible for the disease. However, Tyler & Perkoff (73) have applied new techniques to evaluate endocrine function in these patients and have failed to substantiate the hypothesis.

Several experimental procedures have been developed whereby lesions can be induced in experimental animals which are comparable microscopically to the pathologic lesions observed in human dystrophy. One of these results in the dystrophy shown by vitamin E deficient rabbits, rats, and other animals (74). This deficiency disease has been thoroughly studied in recent years. Besides its responsiveness to administration of vitamin E or its derivatives and the marked creatinuria which occurs, a significant feature is accelerated tissue respiration which is evident both in intact animals and in their tissues. It may be noteworthy that this effect is not observed in tissue homogenates (75). Human muscular dystrophy differs in that it does not respond to treatment with vitamin E and that dystrophic patients usually have abnormally low basal metabolic rates (73). The concept that some essential metabolite of vitamin E cannot be formed by the human dystrophic has been pursued by Milhorat et al. (76 to 79). The obvious merit of this hypothesis has not been confirmed by discovery of such a substance although a number of potential cofactors and metabolites have been studied.

It has been observed that chicks receiving diets deficient in glycine develop a muscular weakness which appears to be similar to human muscular dystrophy. Here, again, administration of either glycine or creatine leads to recovery (80, 81). This is in contrast to the disappointing clinical results that

have been obtained with glycine or gelatin in the human dystrophies. However, the facts that glycine is a precursor of creatine and that creatinuria is characteristic of human dystrophy make attractive the hypothesis that human dystrophy might be the result of an anomaly of the intracellular handling of creatine. Roche *et al.* (82) used isotopic glycine to study creatine synthesis and excretion in a single patient and concluded that there was increased synthesis of creatine as well as an abnormally rapid excretion. Unfortunately, the patient they studied was a rather atypical clinical example of muscular dystrophy and too little clinical information is supplied to evaluate the diagnosis critically; therefore, the significance of the observations remains unclear. More extensive studies with isotopically labelled creatine, its precursors and metabolites, need to be performed in typical patients before the nature of the defect in creatine metabolism in muscular dystrophy is unraveled. A basic biochemical problem of the dystrophies is whether the muscular wasting which occurs leads to the abnormal handling of creatine or whether an abnormality of creatine metabolism causes the muscular wasting. In this regard it may be significant that Melville & Hummel (83) found that in vitamin E deficiency the defect in creatine metabolism occurs before the development of the pathological condition in muscle tissue.

Minot *et al.* (84) reported that urine from dystrophic patients contained labile phosphate and gave reactions indicating the presence of ribose (osazone formation after treatment with yeast). Subsequently they extended these observations and suggested the test for ribose might be used as a clinical test to distinguish between dystrophy and muscular wasting caused by neurological disease (85). They suggested that dystrophic urines may contain ribose-phosphate-nucleic acid complexes derived either from degenerating muscle nuclei or as a result of some metabolic error in the synthesis or retention of these substances. Drew & Selving (86) confirmed the observation that osazones were formed in urine from dystrophic patients in contrast to those from patients with muscular atropy resulting from neurological disease, but also observed positive results in some nondystrophic patients. No rigorous identification of the substance as ribose, as postulated by Minot *et al.*, has been accomplished. Tyler, Sandberg & Armstrong (87) have been unable to detect labile phosphate or any evidence of such a complex in dystrophic urine, and the presence of an osazone-forming substance has not been observed with any consistency. Further evaluation will be required before the test can can be accepted for clinical use.

MULTIPLE SCLEROSIS

The unsolved question concerning the etiological unity or disunity of the many clinical variants of this demyelinating disorder renders difficult an interpretation of work on the problem (88). Therapeutic trials with anticoagulants, ACTH, cortisone, succinate, and a number of other agents have yielded equivocal results, as would be expected with noneffective agents in this disease which is normally characterized by remissions and exacerbations.

The problem of therapeutic trials in multiple sclerosis has been reviewed by Nathanson (89).

A series of studies has been carried out on the relation of geographic areas to the incidence of multiple sclerosis (90, 91), and Swank has noted a statistically significant increase in dietary fat intake in the areas of increased incidence of the disease (92). To follow this lead he and his co-workers performed a series of studies of lipid metabolism in patients with multiple sclerosis. Although levels of serum lipids are not grossly altered and the response of the serum values to low fat intake fell within the normal range (93), paper chromatography demonstrated definite abnormalities in the serum of 17 out of 26 patients (94, 95). In general, those patients who were experiencing remissions had normal patterns in contrast to those whose disease was active. Swank & Hain (96) have studied also the effect of minute emboli in experimental animals in which lesions not dissimilar to those of multiple sclerosis can be produced. On the basis of these studies, they suggested that multiple sclerosis may occur as a rsult of a vascular insufficiency of local areas caused by occlusion of small arterioles by agglutination of the abnormal lipoproteins present during the acute phases of the disease. Finally, Swank (97) treated a series of patients with dietary regimens very low in fat and observed a decrease in the relapse rate. However, as was emphasized earlier, this type of study in multiple sclerosis is fraught with difficulty and the results to date must be viewed as preliminary. Nonetheless, several other studies which suggest an anomaly of fat metabolism have appeared (98, 99) and the consistency of a fairly extensive series of biochemical and physiological data makes the hypothesis attractive.

Other work is in progress in an attempt to evaluate different theories concerning the mechanism of the development of multiple sclerosis; this work has been reviewed elsewhere (100 to 103). Only the genetic studies have yielded definite data which appear to conflict with Swank's hypothesis. McAlpine and others (104, 105, 106) have demonstrated that there is an increased familial incidence of the disorder and that it behaves like a multiple factor or an incompletely penetrant genetic trait. This fact, however, does not rule out the possibility that there is an essential environmental factor for the expression of the genetic trait. Indeed, such a hypothesis is consistent with the observed data on the genetic distribution of the disorder.

WILSON'S DISEASE

Hepatolenticular degeneration was first described as a clinical entity by Wilson in 1912. It has now been shown that it is associated with metabolic abnormalities and is inherited as a recessive gentic trait. In its clinical manifestations, a number of similarities to some of the symptoms in phenylketonuria are observed, although the clinical and biochemical differentiation of the two is simple. In both syndromes the extrapyramidal motor system is the site of the most frequent neurological manifestations and convulsions are sometimes observed. The biochemical abnormalities which have been ob-

served in Wilson's disease are concerned with amino acid excretion and copper metabolism. Up to the present time, no connection between the two abnormalities has been shown, even though both are invariably present in patients with the disorder.

Increased urinary amino acid excretion was demonstrated first by Uzman & Denny-Brown (107) in 1948; subsequent investigations have revealed that the amino aciduria is always present in these patients but not in many other types of chorea and athetosis (108, 109). Many amino acids are excreted in excess amounts (110, 111); these include several which normally are present in negligible amounts. Uzman & Hood (112) were able to demonstrate amino aciduria in siblings of affected children before the onset of clinical manifestations. Serum amino acid levels are normal in total amount as well as in the relative amounts of the different amino acids. Matthews *et al.* (113) found an increased excretion in relation to creatinine clearance after animo acid adminstration. This indicates that the anomaly may occur as the result of a failure in normal renal handling of amino acids. Although it is possible that other tissues do not metabolize amino acids normally, no evidence supporting this idea has been presented.

Study of the abnormality in copper metabolism which occurs in Wilson's disease commenced when Haurowitz (114) demonstrated increased levels of copper in brain and liver tissue of patients with hepatolenticular degeneration. More extensive subsequent studies by Cumings (115) confirmed this finding. In 1948 Mandelbrote *et al.* (116) observed a case of Wilson's disease among a group of patients with demyelinating diseases in which copper metabolism was being studied. They found a high urinary excretion of copper and a marked increase on administration of 2,3-dimercaptopropanol (BAL) but failed to recognize the significance of the finding. The confirmation of the increased excretion of copper by Porter (117) and Cumings (118) stimulated additional investigations of copper metabolism in Wilson's disease.

Reports concerning serum levels of copper have been conflicting (111, 117). Scheinberg & Gitlin (119) have presented evidence which indicates that the copper in sera from patients with hepatolenticular degeneration is not in the form of ceruloplasmin, which contains most of the copper in normal serum. They found that the amounts of this protein were considerably reduced in all of their patients, and that copper was present either in an abnormal form or in increased amounts of some minor normal serum constituent, and suggested that the lack of this protein is the fundamental defect in the disease.

The elevated tissue levels of copper and the availability of 2,3-dimercaptopropanol (BAL), which is known to bind heavy metals and facilitates their excretion, has led a number of investigators to test BAL as a therapeutic agent in this disorder. Denny-Brown & Porter (120), Cumings (118), and Streifler & Feldman (121) have treated patients for short periods and obtained clinical results which are of considerable interest. A moderate to marked improvement occurs in patients with chronic neurologic signs suggestive of basal ganglion lesions. The improvement is delayed in its onset

several days after the beginning of therapy with BAL, although a greatly increased excretion of copper occurs within a few hours after the drug is injected. The remissions induced have never been complete, and some patients have shown relatively little change. Relapse usually has occurred after a few months. Cartwright (122) has observed that that Calsol (Versene) and certain amino acids will cause equally effective copper excretion but no clinical improvement occurs. He has also treated a patient a second time with BAL after relapse had occurred and induced a second significant remission. The effect of long term maintainance therapy with BAL has not been reported. The results of BAL treatment in the more fulminating cases have been disappointing in that relatively insignificant changes have been observed. Denny-Brown has pointed to the fact that more extensive cystic lesions are found pathologically in these cases; these might be expected to be responsible for irreversible changes which are in contrast to the gliosis characteristic of the anatomic lesions in the more chronic cases. No change in amino acid excretion or apparent liver damage has been observed during or after treatment, even in cases where rather striking improvement in mental condition has been observed.

The present knowledge about Wilson's disease suggests that this inherited metabolic disorder involves an abnormality in the renal handling of amino acids and an apparently unrelated disorder of copper metabolism. The latter anomaly must feature an abnormally high absorption of copper from the gastrointestinal tract, otherwise the high tissue and urinary levels could hardly persist in the observed fashion. It is tempting to hypothesize that abnormal copper absorption is the basic defect, with the result that abnormally large amounts of copper accumulate in tissues where it causes anatomic lesions in the areas of maximal concentration; i.e., the liver, the brain, particularly the basal ganglia, and possibly the kidneys. The low values for serum copper reported by some laboratories appears to be in opposition to this hypothesis. However, these might be accounted for by the observed lack of ceruloplasmin, which, in turn, could be the stimulus for an increased absorption of copper. A picture such as this would be consistent with present ideas of inheritance whereby single genes are thought to influence single metabolic reactions. It is difficult to harmonize a possible multiple effect of a single gene defect upon such diverse tissues as brain, liver, and kidney with other evidence obtained with microorganisms, plants, and animals. If this hypothesis were correct, it seems likely that if patients could be identified before hepatic or central nervous system damage were marked, it might be possible to prevent the otherwise inevitable structural damage which leads to disability and death. This might be accomplished by reducing copper intake, by interfering with absorption, or by repetitive treatment with BAL.

LITERATURE CITED

1. Hoskins, R. G., *The Biology of Schizophrenia* (W. W. Norton & Co., Inc., New York, N. Y., 191 pp., 1946)

2. Bellak, L., *Dementia Praecox* (Grune & Stratton, Inc., New York, N. Y., 456 pp., 1948)
3. Gillies, H., *Recent Progress in Psychiatry*, 2, 346 (J. & A. Churchill, Ltd., London, England (1950))
4. Rinkel, M., Deshon, H. J., Hyde, R. W., and Solomon, H. C., *Am. J. Psychiat.*, 108, 572 (1952)
5. Hoch, P. H., Cattell, J. P., and Pennes, H. H., *Am. J. Psychiat.*, 108, 579 (1952)
6. Osmond, H., and Smythies, J., *Mental Sci.*, 98, 309 (1952)
7. Kallmann, F., *The Genetics of Schizophrenia* (J. J. Augustin, New York, N. Y., 291 pp., 1938)
8. Blickenstörfer, E., *Arch. Psychiat. Nervenkrankh*, 188, 226 (1952)
9. Trethowan, W. H., and Cobb, S., *Arch. Neurol. Psychiat.*, 67, 288 (1952)
10. Spillane, J. D., *Brain*, 74, 72 (1951)
11. Reitan, R. M., *Arch. Neurol. Psychiat.*, 69, 4 (1953)
12. Harslof, E., *Ugeskrift Laeger*, 114, 573 (1952)
13. Fitz, T. E., and Hallman, B. L., *Arch. Internal Med.*, 89, 547 (1952)
14. Todd, J., *Brit. Med. J.*, I, 569 (1951)
15. Rome, H. P. and Braceland, F. J., *Am. J. Psychiat.*, 108, 641 (1952)
16. Altschule, M. D., *The Biology of Mental Health and Disease*, 449 (Paul B. Hoefer, Inc., New York, N. Y., 654 pp., 1952)
17. Hoagland, H., Pincus, G., Elmadjian, F., Romanoff, L., Freeman, H., Ballan, J., Berkeley, A., and Carlo, J., *Arch. Neurol. Psychiat.*, 69, 4 (1953)
18. Pincus, G., and Hoagland, H., *Am. J. Psychiat.*, 106, 641 (1950)
19. Tsai, S. Y., Bennett, A., May, L. G., and Gregory, G. L., *Proc. Soc. Exptl. Biol. Med.*, 74, 782 (1950)
20. Altschule, M. D., and Parkhurst, B. H., *Arch. Neurol. Psychiat.*, 64, 516 (1951)
21. Hoagland, H., Callaway, E., Elmadjian, F., and Pincus, G., *Psychosomat. Med.*, 12, 73 (1950)
22. Alexander, S. P., and Neander, J. F., *Arch. Neurol. Psychiat.*, 69, 3 (1953)
23. Dickes, R., Flamm, G. H., Bowman, W., Hollander, E. E., and Potter, H. A., *Am. J. Psychiat.*, 110, 125 (1953)
24. Lindner, T., *Social Medicinsk Tidskrist*, 27, 145 (1950)
25. Gottfriend, S. P., and Minsky, I., *Arch. Neurol. Psychiat.*, 66, 708 (1951)
26. Altschule, M. D., Siegel, E. P., Restaino, R. M., and Parkhurst, B. H., *Arch. Neurol. Psychiat.*, 67, 228 (1952)
27. Bliss, E. L. (Personal Communication, June, 1953)
28. Bush, I. E., and Sandberg, A. A., *J. Biol. Chem.*, 205, 783 (1953)
29. Simon, W., and Garvey, J. T., *Arch. Neurol. Psychiat.*, 65, 717 (1951)
30. Perkoff, G. T., and Tyler, F. H., *Am. J. Med.*, 10, 777 (1951)
31. Meduna, L. J., and Vaichulis, J. A., *Diseases of Nervous System*, 9, 248 (1948)
32. Walker, J. W., and Mayer-Gross, W., *Brit. J. Exptl. Pathol.*, 32, 51 (1951)
33. Morgan, M. S., and Pilgrim, F. J., *Proc. Soc. Exptl. Biol. Med.*, 79, 106 (1952)
34. Mayer-Gross, W., *J. Mental Sci.*, 98, 683 (1952)
35. Quastel, J. H., and Wales, W. T., *Lancet*, I, 402 (1940)
36. Nandi, D. N., *Indian. J. Med. Research*, 40, 295, 303 (1952)
37. Fischer, R., Georgi, F., and Weber, R., *Schweiz. med. Wochschr.*, 81, 817 (1951)
38. Bischoff, A., *Monatsschr. Psychiat. Neurol.*, 124, 211 (1952)
39. Brenner, W., and Breier, A., *Z. Kinderheilk*, 66, 620 (1949)
40. Munch-Petersen, S., *Acta Psychiat. et Neurol.*, 25, 423 (1950)
41. Munkvad, I., *Acta Psychiat. et Neurol.*, 25, 269 (1950)

42. Young, M. K., Jr., Berry, H. K., Beerstecher, E., Jr., and Berry, J. S., *Univ. Texas Publ.*, No. 5109, 189 (1951)
43. Altschule, M. D., and Sulzbach, W. M., *Arch. Neurol. Psychiat.*, **61**, 44 (1949)
44. Henschel, A., Brožek, J., and Keys, A., *J. Appl. Physiol.*, **4**, 340 (1951)
45. Doust, J. W. L., *J. Mental Sci.*, **98**, 143 (1952)
46. Doust, J. W. L., and Schneider, R. A., *J. Mental Sci.*, **98**, 411 (1952)
47. Sackler, M. D., Sackler, R. R., Sackler, A. M., and VanOphuijsin, J. H. W., *Am. J. Psychiat.*, **108**, 669 (1952)
48. Altschule, M. D., and Lorenz, M., *Proc. Soc. Exptl. Biol. Med.*, **71**, 6 (1949)
49. Altschule, M. D., *J. Clin. Exptl. Psychopathol.*, **12**, 123 (1951)
50. Penrose, L. S., *Biology of Mental Defect*, 142 (Sidgwick & Jackson, London, England, 285 pp., 1949)
51. Cowie, V. A., *J. Mental Sci.*, **97**, 505 (1951)
52. Jervis, G. A., *Proc. Soc. Exptl. Biol. Med.*, **82**, 514 (1953)
53. Udenfriend, S., and Bessman, S. P., *J. Biol. Chem.*, **203**, 961 (1953)
54. Cowie, V. A., *Lancet*, **I**, 272 (1951)
55. Jervis, G. A. (Personal communication, August, 1953)
56. Yannet, H. (Personal communication, August, 1953)
57. Fields, W. S. (Personal communication, August, 1953)
58. Armstrong, M. D., and Tyler, F. H. (Unpublished data)
59. Borek, E., Brecher, A., Jervis, G. A., and Waelsch, H., *Proc. Soc. Exptl. Biol. Med.*, **75**, 86 (1950)
60. Jervis, G. A., *Proc. Soc. Exptl. Biol. Med.*, **81**, 715 (1952)
61. Rimington, C., *Brit. J. Nutrition*, **4**, 242 (1950); *Biochem. Soc. Symposia*, *(Cambridge, England)* No. 4, 16 (1950)
62. Woolf, L. I., *Biochem. J. (London)*, **49**, ix (1951)
63. Woolf, L. I., and Vulliany, D. G., *Arch. Disease Childhood*, **26**, 487 (1951)
64. Sherwin, C. P., and Kennard, K. S., *J. Biol. Chem.*, **40**, 260 (1919)
65. Bickel, H., Gerrard, J., and Hickmans, E. M., *Lancet*, **II**, 812 (1953)
66. Jervis, G. A., *Arch. Neurol. Psychiat.*, **38**, 944 (1937)
67. Berry, J. P., and Woolf, L. I., *Nature*, **169**, 202 (1952)
68. Dobriner, K., Rhoads, C. P., and Lieberman, S., *Nutritional Deficiency in Nervous and Mental Disease*, 158 (Williams & Wilkins Co., Baltimore, Md., 215 pp., 1943)
69. Armstrong, M. D. (Unpublished data)
70. Perkoff, G. T., and Tyler, F. H., *Med. Clin. N. Amer.*, **37**, 545 (1953)
71. Tyler, F. H., and Stephens, F. E., *Ann. Internal Med.*, **35**, 169 (1953)
72. Tyler, F. H., and Stephens, F. E., *Ann. Internal Med.*, **32**, 640 (1950)
73. Tyler, F. H., and Perkoff, G. T., *Arch. Internal Med.*, **88**, 175 (1951)
74. Pappenheimer, H. M., *Physiol. Rev.*, **23**, 37 (1943)
75. Hummel, J. P., and Melville, R. S., *J. Biol. Chem.*, **191**, 391 (1951)
76. Milhorat, A. T., and Bartels, W. E., *Federation Proc.*, **6**, 414 (1947)
77. Ulick, S., and Milhorat, A. T., *Science*, **110**, 531 (1949)
78. Milhorat, A. T., Mackenzie, J. B., Ulick, S., Rosenkrantz, H., and Bartels, W. E., *Ann. N. Y. Acad. Sci.*, **52**, 334 (1949)
79. Mackenzie, J. B., Rosenkrantz, H., Ulick, S., and Milhorat, A. T., *J. Biol. Chem.*, **183**, 655 (1950)
80. Almquist, H. J., Mecchi, E., and Kratzer, F. H., *J. Biol. Chem.*, **141**, 365 (1941)
81. Hegsted, D. M., Briggs, G. M., Elvehjem, C. A., and Hart, E. B., *J. Biol. Chem.*, **140**, 191 (1941)

82. Roche, M., Benedict, J. D., Yü, T. F., Bien, E. J., and Stetten, D., Jr., *Metabolism*, **1**, 13 (1952)
83. Melville, R. S., and Hummel, J. P., *J. Biol. Chem.*, **191**, 383 (1951)
84. Minot, A. S., Frank, H., and Dziewiatkowski, D., *Arch. Biochem.*, **20**, 394 (1949)
85. Orr, W. F., and Minot, A. S., *Arch. Neurol. Psychiat.*, **67**, 483 (1952)
86. Drew, A. L., and Selving, B. T., *Neurology*, **3**, 563 (1953)
87. Tyler, F. H., Sandberg, A. A., and Armstrong, M. D. (Unpublished data)
88. Denny-Brown, D., *Amer. J. Med.*, **12**, 501 (1952)
89. Nathanson, M., *Amer. J. Med.*, **12**, 593 (1952)
90. Swank, R. L., Lerstad, O., Strøm, A., and Backer, J., *New Engl. J. Med.*, **246**, 721 (1952)
91. Kurland, L. T., *Am. J. Med.*, **12**, 561 (1952)
92. Swank, R. L., *Am. J. Med. Sci.*, **220**, 421 (1950)
93. Wilmot, V. A., and Swank, R. L., *Amer. J. Med. Sci.*, **223**, 25 (1952)
94. Swank, R. L., Franklin, A. E., and Quastel, J. H., *Proc. Soc. Exptl. Biol. Med.*, **76**, 183 (1951)
95. Swank, R. L., *Arch. Neurol. Psychiat.*, **69**, 281 (1953)
96. Swank, R. L., and Hain, R. F., *J. Neuropathol. Exptl. Neurol.*, **11**, 280 (1952)
97. Swank, R. L., *Arch. Neurol. Psychiat.*, **69**, 91 (1953)
98. Chiavacci, L. V., and Sperry, W. M., *Arch. Neurol. Psychiat.*, **68**, 37 (1952)
99. Fisk, A., Chanutin, A. H., and Klingman, W. O., *Arch. Neurol. Psychiat.*, **67**, 332 (1952)
100. Lesny, I., Polacek, L., and Eichlera, V., *Biol. Agicke Listy*, **32** 175 (1951)
101. Schumacher, G. A., *J. Am. Med. Assoc.*, **143**, 1059 (1950)
102. Schumacher, G. A., *J. Am. Med. Assoc.*, **143**, 1241 (1950)
103. Reese, H. H., *Am. J. Med.*, **12**, 572 (1952)
104. McAlpine, D., and Compston, N., *Quart. J. Med.*, **21**, 135 (1952)
105. Pratt, R. T. C., Compston, N. D., and McAlpine, D., *Brain*, **74**, 191 (1951)
106. Mackay, R. P., *Research Publ. Assoc. Research Nervous Mental Disease*, **28**, 150 (1950)
107. Uzman, L., and Denny-Brown, D., *Am. J. Med. Sci.*, **215**, 509 (1948)
108. Porter, H., *J. Lab. Clin. Med.*, **34**, 1623 (1949)
109. Spillane, J. D., Keyser, J. W., and Parker, R. A., *J. Clin. Pathol.*, **5**, 16 (1952)
110. Cooper, A. M., Eckhardt, R. D., Fallron, W. W., and Davidson, C. S., *J. Clin. Invest.*, **29**, 265 (1950)
111. Beam, A. G., and Kunkel, H. G., *J. Clin. Invest.*, **31**, 616 (1952)
112. Uzman, L., and Hood, B., *Am. J. Med. Sci.*, **223**, 392 (1952)
113. Matthews, W. B., Milne, M. D., and Bell, M., *Quart. J. Med.*, **21**, 425 (1952)
114. Haurowitz, F., *Hoppe-Seyler's Z. physiol. Chem.*, **190**, 72 (1930)
115. Cumings, J. N., *Brain*, **71**, 410 (1948)
116. Mandelbrote, B. M., Stanier, M. W., Thompson, R. H. S., and Thurston, M. N., *Brain*, **71**, 212 (1948)
117. Porter, H., *Arch. Biochem. and Biophys.*, **31**, 262 (1951)
118. Cumings, J. N., *Brain*, **74**, 10 (1951)
119. Scheinberg, I. H., and Gitlin, D., *Science*, **116**, 484 (1952)
120. Denny-Brown, D., and Porter, H., *New Engl. J. Med.*, **245**, 917 (1951)
121. Streifler, M., and Feldman, S., *Arch. Neurol. Psychiat.*, **69**, 1 (1953)
122. Cartwright, G. E. (Personal communication, September, 1953)

PSYCHIATRY[1,2]

By Robert G. Heath

Tulane University School of Medicine, New Orleans, Louisiana

General Introduction

During 1952 and the beginning of 1953 the advancements made in psychiatry were inconspicuous and came for the most part from other specialties. Nothing was published citing startling therapeutic advances as a result of new technique. For the most part it was difficult to find anything in the psychiatric literature which could be classified as new information or a definite advancement. In this author's opinion those advancements that appear to be most significant came largely from the fields of basic physiology and chemistry and in the evolution of newer approaches in internal medicine. Changes were taking place in the concept of psychiatric education. These, by and large, were the advancement of ideas for better correlation among related specialties aimed at a better understanding and more effective approach to the problems of human behavior. In the psychiatric literature one sees to a greater extent than in preceding years, a tendency to allude frequently, in a somewhat sketchy detached manner, to basic researches and apparently a more realistic awareness that advances in other fields are important to psychiatry.

Since in this review the author has considerable latitude as to the particular aspects of the field he cares to discuss and in the space allotted it is impossible to cover the field completely, the major discussion will be centered upon the relationship of advances in the basic sciences to an understanding of human behavior, and the new trends in the concepts of psychiatric education. Other areas of the field will be mentioned more briefly.

Behavior and Research in the Basic Sciences

During the past year mention has been made in several psychiatric articles of some of the recent physiological and biochemical research work with an implied recognition that the findings in these basic areas might have significance in leading ultimately to greater understanding of psychology (1, 2, 3).

In reference to physiological research.—Psychiatrists have made special reference to the work of Magoun and associates, who have worked with the reticular activating system of the brain. In most of these references there is a tendency to surround this region with a magical aura. By and large, when discussing the reticular activating system, the authors attempt to justify their pet physiological theories. In no instance in the psychiatric literature has any testable hypothesis been advanced to correlate or cross-interpret

---

[1] The survey of literature pertaining to this review was concluded in August, 1953.

[2] The following abbreviations are used: EEG for electroencephalogram; GAP for Group for the Advancement of Psychiatry.

223

the findings obtained by the psychiatric techniques and those obtained by the psychological techniques. It seems that the principal advantage from this trend in psychiatry is limited to the fact that some psychiatrists are becoming aware of and are doing some reading of the basic physiological literature. The absence of testable hypotheses, a tendency that has always characterized psychiatric literature, is to be criticized.

In the work of Magoun & co-workers (4 to 10), several very interesting and provocative findings have been described. Stimulation of a central core of the midbrain medial to the direct sensory pathways and extending from the pons to the posterior thalamic region has resulted in an alerting response characterized by desynchronization of the EEG. The authors have found through recordings that various types of sensory stimuli will fire this region in a manner different to the way in which the direct sensory pathways are fired. Lesions in this region have resulted in akinesia, a picture of somnolence, failure of response to sensory stimuli, and increased slow wave activity on electrocortical recordings (4, 5).

French (11) has also reported the symptoms of akinetic mutism and stupor in three patients who had lesions in this region associated with diffuse brain damage, as well as in two patients who had lesions that seemingly interrupted the pathway to the cortex from this area.

The importance of wakefulness or alerting in behavior disorders is obvious. Attempts, however, to tie in these basic observations with concepts of libido in psychoanalysis appear very weak and certainly offer no testable hypotheses. Jasper & co-workers (12) have made some interesting observations on levels of awareness. They describe a patient with narcolepsy who did not respond to conventional sensory stimuli, for example, loud noises, but who did respond by awakening when her name was whispered to her. It was postulated from this that corticofugal impulses must play an important role in the subcortical activating system. Jasper describes many of the cortical-subcortical pathways identified by means of electrical stimulation and recording.

Although the activating system is referred to in the psychiatric literature, it should be equally important from observations in behavior to consider the possibility of the existence of subcortical regions having an opposite effect, namely, reduction in levels of awareness. It is known that patients suffering from various psychiatric disorders will often display diminution in levels of awareness. There are several references, in the physiological literature, to regions of the brain which when stimulated seemingly result in sleepiness or diminution of awareness (13 to 21). King (22) and Huston (23) have independently described retardation in motor response in schizophrenic patients.

Clinical psychiatric observations and levels of awareness.—In the psychiatric literature there is considerable provocative data to indicate that a physiological procedure, which alters levels of awareness, may open possibilities for cross-interpretation between physiology and psychiatry.

Alterations in thought activity occurring with changes of consciousness

were first described at length by Freud in his studies of dreams (24, 25). In these studies he observed that during periods of diminished awareness the so-called primary processes or deeply unconscious material, appeared in the form of dreams. The emotional wishful self-centered thought characteristic of dreams is also characteristic of much neurotic behavior. The visions and sounds unrelated to reality that occur in dreams are similar to hallucinations that occur in the schizophrenic. The factor of stress in producing inferior behavior patterns was first noted by Freud, especially in some of his later publications (26). In his paper "Emergency Behavior," Rado (27) describes neurosis in the context of faulty emergency reactions to everyday situations as a result of past experiences in the child-parent relationship (28).

Articles concerned with evolution indicate that the ability to anticipate the present and future in terms of past experiences is a behavior characteristic that occurs with evolution of the newer cortex (29). Cobb (30) has attempted to correlate some of the basic and clinical data in a recent article entitled "On the Nature and Locus of Mind." Walter (31), in "Living Brain," offers an interesting speculative approach to mind-brain problems. His thesis is essentially that newer electronic techniques properly applied would make it possible to mirror activity of the brain in association with behavioral patterns. Reference is made to American psychiatry as follows:

It may be assumed that no mental theory or practice is likely to survive which does not take into account the principles of cerebral functions revealed by physiology any more than the practice of medicine can ignore other physical functions. Already the new type of psychiatrist, in touch with centres of physiological research, has adopted a new outlook. The impact has not yet reached the great conservative body of that profession, and perhaps never will do so, especially in the United States, where psychiatry spread in a sweet flood of affluence and crystallized hard. But one may look forward with certainty to the time when brain physiology will be at least as much of a prescribed subject for the psychological and medical student as general physiology is for the latter today.

It is hoped that the results of some of the newer trends this author has attempted to point out, will invalidate such a statement in the near future.

Correlative studies between physiology and psychiatry.—The use of physiological techniques, in conjunction with reporting techniques, have been described by several persons. Walter (31) presents some clinical data correlating EEG[2] activity with emotional stirring. Theta activity (slow, synchronous) appeared with intense emotional responses of the patient. Ostow (32) describes changes in the EEG in association with different affects in a patient who previously showed electrical abnormalities in the temporal lobe as the result of a brain tumor.

The administration of various drugs which alter levels of awareness is proving a rather useful method of correlating physiological and psychological data. Several studies of this type were reported during the past year (3, 33, 34, 35). In general, two main categories of drugs have been investigated, those that fall into the sedative-hypnotic group and another group which

tends to produce psychotic-like behavior (dextrolysergic acid and mescaline). Wikler (3) in particular has offered some interesting formulations as to the relationship between the mechanism of drugs and personality function. His clinical work is augmented by various physiological laboratory experiments.

Chemistry and behavior.—The importance of the internal chemical milieu is being stressed by many investigators from the field of internal medicine (36, 37). This type of investigation points out the importance of the total adaptation of the individual. It has been well established that emotional stress results in changes in body chemistry which are of importance in the maintenance of health or appearance of disease. Papers which discuss behavior changes in association with the administration of steroids continued to appear in large numbers. Some beginning attempts have been made to correlate more closely the chemical changes with altered physiology of the nervous system (38).

Other investigators have concerned themselves with correlations between behavior disorders and the chemistry of immunity. An interesting article is that of Jacobs *et al.* (39) on the proteolytic enzyme inhibitor in the serum of schizophrenic patients. They report that abnormally high rennin titers are encountered in patients with marked dissociated symptoms, largely the hebephrenic-catatonic group (functioning at a markedly reduced level of awareness). These findings may prove to be of importance when considered with Lewis' statistical report (40) that the retarded schizophrenic group shows considerably lower incidence of cancer than the expected rate in the general population. Studies of the type reported by Loumos (41) on the relationship between autonomic nervous system activity and agglutination titers may shed some light on such perplexing problems as the reason for the high incidence of tuberculosis in schizophrenic patients (42).

THERAPY

Psychotherapy.—Even though no spectacular claims for new treatments were made during the past year, there was a healthy trend in the field which is apparent in several publications. This trend has been toward a more realistic appraisal of the effects of psychotherapy. Several authors have pointed out the need for better techniques of evaluation of the psychotherapeutic process, and also the relative absence at present of testable hypotheses that would lead to a better understanding of the psychotherapeutic process. The latest monograph of the *Association for Research in Nervous and Mental Disease*, which was devoted to psychiatric treatment, was published early in 1953. In it appear several valuable papers which present in a forthright manner the perplexing problems surrounding psychiatric treatment.

Wortis (43) states, "A survey of the reports indicates that the therapist should be humble in claims made for the exclusive effectiveness of any one treatment procedure or for any one factor influencing treatment in psychiatry." Appel *et al.* (44) in discussing long term psychotherapy reviews the published results through use of the different psychotherapeutic approaches. From this he draws two possible conclusions as to why different types of

psychotherapy are approximately equal in effect. First, that psychotherapy had no effect on the patient; second, that the nonspecific and common elements of the different types of treatment grossly outweigh the individual differences. In discussing the first possibility, that psychotherapy has no effect, Appel states,

Is there an underlying pathological process which is untouched and uninfluenced by therapy? Would all the cases have shown the same recovery rate had no therapist been seen and no therapy instituted? Does the whole idea of the usefulness of psychotherapy merely fulfill the therapist's need to feel secure, to feel that he is doing something, or to satisfy his need for power and domination? We know of no statistics concerning the spontaneous course of these reactions which can be used to refute this possibility. This would in essence deny that the patient can be influenced by psychological means, deny that his anxieties can be aroused or allayed by the doings, feelings or saying of the therapist. This is contrary to experience.

The second and more probable conclusion is then that the common features of the various types of psychotherapy are of far greater importance than the individual differences. The non-specific elements of therapy seem to be more important than the intellectual formulations the therapist uses. Therapy is more basic than our theories.

The action of and the need for long term followups on patients, and a satisfactory evaluation of the spontaneous course in various behavior disorders, is pointed up by several other authors. One example of difficulties encountered when attempting to evaluate the therapeutic process is apparent in an article by Reid & Finesinger (45) entitled "The Role of Insight in Psychotherapy." The term insight is loosely bantered about in the field. The authors make it apparent that it is extremely difficult to determine the effectiveness of insight in producing clinical improvement with psychotherapy. Difficulties are encountered in defining and describing what happens to a person in response to an interpretation in therapy. The authors make it clear that considerably more concern is required on the part of serious workers in the field in order to understand the role of insight. They too point out the need for the formulation of hypotheses that are subject to more accurate testing than the present ones in psychiatric theory. They conclude that there is a serious need for more objective data gathering through the use of logical hypotheses before the role of insight can be settled.

Although there were several articles dealing with the subject of technique in psychoanalytic therapy, I will, for the purposes of this review, discuss at length only two, since together they seem to cover the divergent viewpoints.

The first article by Rado (28) is entitled "Recent Advances of Psychoanalytic Therapy." In this article Rado describes the adaptational technique which he considers a consistent development of the classical theory. His approach offers hypotheses that are certainly more subject to testing than those offered by previous psychoanalytic techniques and promises to shed light on therapeutic mechanisms by which various treatment procedures operate.

Doctor-patient relationships in therapy are presented in terms of the parent-child patterns. In this over-all context he mentions the characteristic patterns developed with different types of psychotherapeutic methods, from hypnotherapy to the two psychoanalytic therapies (the classical technique and the adaptational technique). In hypnotherapy there is a reinforcement of the parent to child relationship. In Freud's cathartic method, or the classical psychoanalytic technique which in essence consisted of the discovery of parentified treatment, the patient's emotional relationship to the physician was first made apparent. This was posed as the crucial problem of all psychotherapy.

Rado's criticism of the classical method was that it re-introduced an authoritative principle in the treatment of the patient, since in the transference the patient continued to practice his child-like emotional dependence throughout the treatment. Critics feel that the classical technique offered no method for modifying the dependency. Another criticism was that it tended to concentrate all interests and efforts on the patient's past to the neglect of his present adaptation.

Rado states that the goal of psychoanalysis should be total reconstruction designed to permit the patient to work at the self-reliant level. In essence it was felt that the patient, to function at this level, must learn to understand his doings in terms of motivation and control, to evaluate his doings in terms of the cultural contact, and to understand his development in terms of his background and life history. The maximum goal of therapy should be to improve the patient's adaptation to the here and now. Rado suggests methods to accomplish this aim.

Zilboorg (46) illustrates the classical technique. He comments in his article that "there is much to be clarified, more to be restudied and relearned in all this, for since Freud introduced ego psychology little further has been contributed except the articles of Waelder and of Nunberg on the integrative and multiple functions of the ego."

In his article he follows this theme in that he adds nothing beyond Freud's contributions and, in fact, there is a notable absence of the enlightened critique and awareness of the difficulties that Freud presented in association with this technique (47, 48). Freud pointed out the transference phenomenon and described progress in analysis as taking place in the context of the patient's relating to the therapist as a "good child," Freud emphasized the difficulties encountered in terminating treatment as a result of this relationship, first pondering the problem as to how, after the patient gained insight, was he to put it into use in an adult manner and finally concluding that he could see no way out of the morass developing as a result of the dependent transference relationship. In contrast to Freud, Zilboorg evidently considers this dependent relationship as therapeutic. To illustrate this he discusses a patient as follows:

The patient of forty who adopted his analyst's necktie and lived out a good part of his cross-identification and the conflicts contained therein succeeded in living it all out via a partially hostile (at any rate ambivalent) identification with the ana-

lyst, and via a strong emotional relationship to and with the analyst. By calling attention to this obvious fact, I want to say that the whole problem of ego reliving and ego redintegration is in the final analysis a problem of causing it to be relived in the transference. It must never be forgotten that the analyst during the period of treatment is the only true reality through which the ego can safely experiment with the process of integration. By this I mean to say that the phenomenon and the dynamics of transference have become even more vital and more complex since the advent of ego psychology into psychoanalysis. It is, therefore, technically erroneous from the standpoint of therapy, and especially from the point of view of psychoanalytic education, to relate the problems of transference almost exclusively to infantile sexuality or infantile experiences. Transference has been extended and deepened under the influence of ego psychology, and I would not hesitate to state with utmost emphasis that insight through transference is the only type of insight which serves the purpose of reorientation and redintegration of the ego. Such insight is a purely affective process in the wake of which follows rational and affective appreciation of a new orientation of the ego toward the world and toward one's own self. Without the transference the process of gaining insight leaves only a series of conceptual props for the ego. The ego is bound to use these props, and at that only temporarily, to reinforce its habitual defenses.

Zilboorg does not explain the all important step as to how insight through transference leads to rational and effective appreciation of a new orientation towards the world.

It is well known that many patients as a result of analysis become more and more dependent upon the analyst and less able to make independent decisions. The technique herein described might explain the mechanism by which this bondage relationship occurs (28). An interesting sidelight is that the schizophrenic patient is known to function through identification with his therapist because of the inherent nature of his pathology. It would seem the encouragement of this excessive dependency might serve as useful therapy for the schizophrenic and, indeed, it is now known that many of Freud's older patients proved to be schizophrenic (49). This may be an important mechanism accounting for improvement in many of his early cases.

In this same article Zilboorg discusses the role of insight, implying that in some way a compulsive repetition of this dependency relationship to the therapist would lead to a lasting insight. Throughout much of the psychoanalytic literature as in this case, we see the previously mentioned absence of testable hypotheses (45), particularly in this important realm of technique.

Areas of agreement and disagreement between the adaptational and classical techniques can be summarized as follows; in both, the transference phenomenon is fully recognized. The difference lies in the manner in which transference is used. With the classical technique the repetition compulsion of the transference is considered to be therapeutic. Rado denies that this in itself is effective therapy, and points out complications that can occur in this relationship. The adaptational technique is described as a method of avoiding the pitfalls and thereby utilizing the transference for more effective treatment.

Psychoanalysis represents a technique which utilizes to a maximum degree the reporting of the patient. This should be our most valuable tool in understanding behavior in the human. It is the hope of many in the field that hypotheses can be established so that the reporting technique may lead to greater understanding, not only of psychotherapy, but all forms of therapy directed towards the treatment of human behavior disorders. Other authors have commented on the need for concentration on improving the patient's present adaptive patterns in terms of the existing cultural milieu (50).

Schizophrenia remains the major unsolved problem, accounting for the majority of patients in mental hospitals. Although greater energy is going into research towards understanding and developing treatment for this disorder, these efforts are still feeble when compared to the magnitude of the problem. A valuable paper concerned with a 30 year followup of 141 mental patients appeared in 1952 (51). Such long term studies are an important foundation for all research efforts. It is noteworthy that in the literature this disease was approached through the utilization of many varied techniques, including psychotherapy, biochemistry, physiology, academic psychology (22), and genetics. It is apparent from the cold statistics that virtually no progress has been made towards the development of a significantly effective therapy for schizophrenia.

Cortical surgery.—The literature continues to be filled with references to current psychosurgical procedures. It seems that in no instance have new ideas been forthcoming. The articles by and large deal with statistical reviews of the effects of undercutting or ablation of the cortex and a recapitulation of some psychological findings following the procedures. There has also been some discussion of minor differences occurring with alterations of the surgical technique (52, 53, 54). Obviously some enthusiasm still continues. It is apparent that some patients will improve so far as social functioning is concerned following the current psychosurgical procedures, and it is also very apparent that such destructive procedures add but little to our therapeutic armamentarium.

Data gathered through these procedures have no doubt contributed something toward the understanding of human behavior. The findings recorded recently, however, have been previously reported over the past several years. The basic change that appears to occur following these operations is a lessening of concern for the future. This manifests itself by alterations to varying degrees of many symptoms depending upon the manner in which the individual is suffering.

Data reported from the field of evolution and comparative psychology are in some ways consistent with this observation. Von Bonin (29) reports that the most obvious difference between the brain of man and monkey is the extensive development of the frontal and temporal cortex. The principal behavioral characteristic accompanying this anatomical development is the ability to anticipate the distant future in terms of past events (memory). Penfield's (55) stimulation experiments give interesting suggestive confirma-

tion of this observation. Perhaps this consistently observed behavioral change following cortical destruction can form an important cornerstone to further research.

Electro-convulsive therapy.—The electro-convulsive therapies retain approximately the same place in the field of psychiatry that they have over the past five to ten years. This type of therapy continues to be recognized by and large as a palliative measure, having its greatest immediate effectiveness in the shortening of the course of depressive reactions. Its greatest therapeutic effectiveness is in the treatment of those patients who have adapted quite satisfactorily prior to the onset of depression in late middle age. The changes in technique described over the past year have been minor. From the standpoint of contributing to the understanding of behavioral problems this procedure with diffuse stiiulations of the entire brain is of little or no use.

The criticisms advanced in previous years (56) regarding the ways in which electroshock is sometimes abused in the current practice of psychiatry are still quite valid. No evidence has been forthcoming to show that electroshock is much more than a palliative. It does not alter basic adaptive patterns and must, if maximum benefit is to be gained, be supplemented by psychotherapy.

TRAINING IN PSYCHIATRY

Recently there has been an upsurge of interest in the subject of methods of training in psychiatry. This interest and some recent innovations offer considerable promise for improvement in training methods in the future.

Training in psychiatry has differed in many respects from training in other specialties. Some of this no doubt is attributable to the nature of the subject material. Also, psychiatry is a new specialty, only recently taking its place in the family of medical disciplines. The nature of the training programs has no doubt contributed to some of the lag in the development of understanding of many crucial problems mentioned earlier.

One of the chief factors retarding progress has probably been the lack of integration of various technical approaches. Psychiatry is a unique specialty in that in many ways it serves as a bridge between the medical-biological sciences and the social sciences. Several publications recently have pointed out the lack of integration of the different approaches and emphasized a need for closer correlation. Various articles, likewise, point out a trend towards better integration. The proceedings of the Second Research Conference on Psychiatric Education held in 1952 have not yet appeared. In last year's *Annual Review of Medicine*, Rennie (57) mentioned the Conference and the major topics discussed. Whitehorn (58) gave a brief summary of the nature of this Conference and focused attention upon some of its highlights.

In his academic address to the American Psychiatric Association, Whitehorn (59) made an appeal for more comprehensive integrated teaching in medicine and the field of psychiatry. He specifically emphasized the paradoxical dichotomy existing between psychiatric and psychoanalytic training

and made an appeal for integration of the clinical sciences of psychiatry with the basic sciences. Others (60, 61) noted the necessity for the inclusion of the social sciences into medicine through psychiatry. For a more comprehensive review of the subject of integration of social sciences into medicine see Rennie's review (57). Progress in this direction is valuable not only for psychiatry, but also for the social sciences, since the psychiatric clinics and wards can provide the social sciences with valuable clinical material for their investigations, thereby serving as a type of practical laboratory.

An appeal for less isolation and greater integration with other specialties of medicine was also forthcoming in regard to the child psychiatry programs. Levy (62), in reviewing the history of the child psychiatry movement, indicated that the isolated Guidance Center should be more closely integrated with the hospitals and pediatrics services.

Several articles dealt with the dichotomy between the training programs in psychiatry and psychoanalysis. Potter & Klein (63) report a statistical survey of the replies of residents in psychiatric training to questions regarding their interest in psychoanalysis. They found that all residents in training in psychiatry were interested in having psychoanalytic training. The attitude conveyed was that this training would offer them a more effective tool for conducting therapy and understanding behavior. Cameron (61) comments in his article that it seems peculiar to conduct psychiatric clinics in one institution and then travel to another for psychoanalytic training. There are descriptions of programs which tended to lessen this dichotomy. Brosen (64) described the Associated Psychiatric Facilities of Chicago Experiment where an attempt is underway to integrate the psychoanalytic training facilities for residents from several psychiatric training centers. The author points out the need for more training and interest in basic investigation and states, "The advantage of University affiliation to promote these objectives seems apparent."

The preliminary report of the GAP[2] Committee on Medical Education (65) regarding the psychiatric residency training program devotes a section to the "Role of Psychoanalysis in Psychiatric Training." The subject is approached historically, mentioning the growing interest in psychoanalytic training evidenced among trainees in psychiatry. It points out that until recently, dynamic psychiatry and the teaching of psychoanalytic theory was not emphasized in residency programs, but that this is now changing.

Various types of programs directed towards integration of psychoanalytic and psychiatric training are described. It is noted that many residency programs have reorganized their curriculums to include psychodynamics. In other instances, residency programs continue to accept psychoanalytic training for psychoanalytic theory and technique and make time for the residents to attend institutes for this training, thereby encouraging it. A few centers recently have instituted modified training programs. In one program of this type, the psychoanalytic institute has assumed responsibility for comprehensive training by including in its required curriculum organized courses in clinical psychiatry and allied topics in addition to the teaching of psycho-

analytic theory and technique as prescribed for qualified psychoanalytic institutes. Another innovation is the combined selection of applicants for residency training by the training center and the psychoanalytic institute. Under this system the candidates selected by the psychoanalytic institute for subsequent training are drawn predominantly from the cooperating residency programs. In another plan, the department of psychiatry is attempting to develop a program within the department for training in both psychiatry and psychoanalysis, as well as the basic sciences, for all residents. In this instance the formal psychoanalytic institute would be completely eliminated.

The tentative GAP report closes with the following remarks.

The current trend toward integration of psychoanalytic and psychiatric training seems not only inevitable but constructive. Various methods of implementing such integration are being explored, but at present there are insufficient data regarding the effectiveness of any single method. However, there is general agreement among the committee members that residency programs should combine training in clinical psychiatry with psychoanalytic theory for all residents, but it should not necessarily include the technique of psychoanalysis. The committee would encourage experimental teaching of the technique of psychoanalysis within the residency training period. The most preferable method for the teaching of psychodynamics, including psychoanalytic theory, is in close relationship with appropriate on-the-spot supervision of residents in their daily management and therapeutic activities. Obviously this can be done only where teachers are qualified to teach theory and its clinical application as a unified whole.

The GAP report does not represent the thinking of all persons in psychiatry and psychoanalysis. A peculiar paradox still exists in that one phase of our specialty, namely, psychonalysis, still is taught almost exclusively outside of the university medical center. In fact, only teaching in so-called institutes is officially approved by the American Psychoanalytic Association. This type of program is justified by the Society on the basis that only they can maintain adequate standards.

In a factual article describing the status of organized psychoanalysis in the United States, Knight (66) gives the history of the psychoanalytic movement and appraises many of the present problems. In regard to training he states,

We do, as an Association, have a responsibility with regard to training done by members outside the jurisdiction of the Association. We have adopted the principle that training in therapeutic psychoanalysis is the function of the authorized institutes of the Association and not of the training analyst as an individual, and have resolved that it shall be against the policy of the Association for any member to train or supervise any individual in psychoanalytic technique except under the direct auspices of a recognized training institute of this Association. Steps are being taken to implement this principle so as to make observance of it one of the conditions for continuation of membership in the Association. The full responsibility of the Association underlies the conferring of membership on graduates of approved institutes, and we have come to regard membership as equivalent to certification in a specialty within a specialty. Unless and until we devise a superior method of certification for psychoanalytic practice our membership standards must be maintained at a high level.

To the best knowledge of this author, this is the only instance in which a society regards membership as equivalent to certification. Moreover, it is seemingly the only instance in which an association in essence dictates that education in what is considered a medical discipline is denied to even the university medical schools.

Knight realistically comments on some of the difficulties present in the psychoanalytic movement.

The spectacle of a national association of physicians and scientists feuding with each other over training standards and practices, and calling each other orthodox and conservative or deviant and dissident, is not an attractive one, to say the least. Such terms belong to religions, or to fanatical political movements, and not to science and medicine. Psychoanalysis should be neither a "doctrine" nor a "party line." Perhaps we are still standing too much in the shadow of that giant, Sigmund Freud, to permit ourselves to view psychoanalysis as a science of the mind rather than as the doctrine of a founder.

He makes some remarks concerning the state of scientific objectivity in the field.

It may take a decade or so to arrive at a point of scientific objectivity regarding psychoanalysis as (1) a research method; (2) a collection of hypotheses which are forever subject to retesting; (3) a body of knowledge obtained through the research method and in the light of the hypotheses; and (4) a technique of treatment of psychological disorders, which is not set once and for all by its original form, but which forever evolves as the intuition, resourcefulness, and artistry of treatment today are reduced to the scientific techniques of tomorrow.

This author wonders if these objectives can be obtained if psychoanalytic training continues as it now exists within the Association. It seems possible that this attitude regarding training may be by and large responsible for the lack of objectivity, the absence of the hypotheses that can be subject to proof, and the complete lack of integration of the various scientific disciplines for the study of human behavior.

The university has always been considered the logical center for education and scientific research. In commenting on the university and science Warren (67) says, "Science is naturally at home in the university, because there the concern is with ultimate truths and the meaning of things, in their development for this generation, and also for their transmission to the generations to come."

On commenting on the role of research Warren states, "Without new basic facts, refinement in technical achievement is forced more and more to minutiae and becomes self-sterilizing."

One cannot help wonder if it would not be valuable from the standpoint of all disciplines if a more objective scientific approach were used in the investigation of problems of human behavior. It seems that more complete awareness and understanding, and contact with workers in such related basic sciences as physiology, biochemistry, neurology, as well as the social sciences, might further the researches of the psychotherapist and psychoanalyst. It too seems highly probable that awareness of the data gained by the psy-

chotherapist and psychoanalyst in regard to behavior disorders would open new and more valuable areas of research for the basic and social sciences.

Consideration of problems highlighted by this review reminds one of a report (68) that "Prof. R. W. Wood, physicist of Johns Hopkins, was asked to respond to the toast 'Physics and Metaphysics' at a dinner of some philosophical society. His response was somewhat as follows: 'The physicist gets an idea which seems to him to be good. The more he mulls over it the better the idea appears. He goes to the library and reads on the subject and the more he reads the more truth he can see in his idea. Finally he devises an experimental test and goes to his laboratory to apply it. As a result of long and careful experimental checking he discards the idea as worthless. Unfortunately,' Professor Wood is said to have concluded, 'the metaphysician has no laboratory'."

LITERATURE CITED

1. Linn, L., *Am. J. Psychiat.*, **110**, 61–62 (1953)
2. Kubie, L. S., *Psychoanal. Quart.*, **22**, 21–52 (1953)
3. Wikler, A., *Am. J. Psychiat.*, **108**, 590–99 (1952)
4. Lindsley, D. B., Bowden, J., and Magoun, H. W., *EEG Clin. Neurophysiol.*, **1**, 475–86 (1949)
5. French, J. D., Von Amerongen, F. K., and Magoun, H. W., *Arch. Neurol. Psychiat.*, **68**, 577–90 (1952)
6. Magoun, H. W., *Epilepsia*, **1**, 69–82 (1952)
7. Magoun, H. W., *Arch. Neurol. Psychiat.*, **67**, 145–54 (1952)
8. Moruzzi, G., and Magoun, H. W., *EEG Clin. Neurophysiol.*, **1**, 455–73 (1949)
9. Starzl, T. E., Taylor, C. W., and Magoun, H. W., *J. Neurophysiol.*, **14**, 461–77 (1951)
10. Rhines, R., and Magoun, H. W., *J. Neurophysiol.*, **9**, 219–29 (1946)
11. French, J. D., *Arch. Neurol. Psychiat.*, **68**, 727–40 (1952)
12. Jasper, H., Ajmone-Marsan, C., and Stoll, J., *Arch. Neurol. Psychiat.*, **67**, 155–66 (1952)
13. Hodes, R., Peacock, S. M., Jr., and Heath, R. G., *Trans. Am. Neurol. Assoc.*, **75**, 194–96 (1950)
14. Hodes, R., Peacock, S. M., Jr., and Heath, R. G., *J. Comp. Neurol.*, **94**, 381–408 (1951)
15. Hodes, R., Heath, R. G., and Hendley, C. D., *Trans. Am. Neurol. Assoc.*, **77**, 201–4 (1952)
16. Peacock, S. M., Jr., and Heath, R. G., *Trans. Am. Neurol. Assoc.*, **77**, 250–84 (1952)
17. Heath, R. G., and Hodes, R., *Trans. Am. Neurol. Assoc.*, **77**, 204–5 (1952)
18. Kaada, B. R., *Ann. Rev. Physiol.*, **15**, 39–62 (1953)
19. Hess, R., Akert, K., and Koella, W., *Rev. neurol.*, **83**, 537–44 (1950)
20. Knott, J. R., Hayne, R., and Meyers, H. R., *Arch. Neurol. Psychiat.*, **63**, 526–27 (1950)
21. Akert, K., and Andersson, B., *Acta Physiol. Scand.*, **22**, 281–98 (1951)
22. King, H. E., *Bull. Tulane Univ. Louisiana Med. Fac.*, **2**, 34–37 (1951)
23. Huston, P. E., and Senf, R., *Am. J. Psychiat.*, **109**, 131–38 (1952)
24. Freud, S., *An Outline of Psychoanalysis*, 46–57 (W. W. Norton & Co., Inc., New York, N. Y., 127 pp., 1949. Published in German, 1940)
25. Freud, S., *Basic Writings* (Modern Library, New York, N. Y., 1001 pp., 1938)
26. Freud, S., *The Problem of Anxiety* (W. W. Norton & Co., Inc., 127 pp., 1936)

27. Rado, S., *Anxiety*, 150–75 (Grune & Stratton, New York, N. Y., 254 pp., 1950)
28. Rado, S., *Research Publs., Assoc. Research Nervous Mental Disease*, **31**, 42–58 (1953)
29. von Bonin, G., *Arch. Neurol. Psychiat.*, **67**, 135–44 (1952)
30. Cobb, S., *Arch. Neurol. Psychiat.*, **67**, 172–77 (1952)
31. Walter, W. G., *The Living Brain* (W. W. Norton & Co., Inc., New York, N. Y., 311 pp., 1953)
32. Ostow, M., *Am. J. Psychiat.*, **110**, 55–60 (1953)
33. Cleghorn, R. A., *Am. J. Psychiat.*, **108**, 568–70 (1952)
34. Rinkel, M., Deshon, J. J., Hyde, R. W., and Solomon, H. C., *Am. J. Psychiat.*, **108**, 572–77 (1952)
35. Hoch, P., Cattell, J. P., and Pennes, H. H., *Am. J. Psychiat.*, **108**, 579–84 (1952)
36. Selye, H., *Stress* (ACTA Inc., Montreal, Canada, 822 pp., 1950)
37. Albright, F., *Bull. N. Y., Acad. Med.*, **29**, 5–10 (1953)
38. Porter, R. W., *Am. J. Physiol.*, **169**, 629–37 (1952)
39. Jacobs, J. S. L., and Tempereau, C. E., *Arch. Neurol. Psychiat.*, **68**, 388–92 (1952)
40. Lewis, N. D. C., *N. Y. Natl. Committee Mental Hygiene* (1936)
41. Loumos, S., *Arch. Neurol. Psychiat.*, **68**, 69–77 (1952)
42. Ferrara, M. A., *New Engl. J. Med.*, **246**, 55–56 (1952)
43. Wortis, S. B., *Research Publs., Assoc. Research Nervous Mental Disease*, **31**, 451 (1953)
44. Appel, K. E., Lhamon, W. T., Meyers, J. M., and Harvey, W. A., *Research Publs., Assoc. Research Nervous Mental Disease*, **31**, 21–34 (1953)
45. Reid, J. W., and Finesinger, J. E., *Am. J. Psychiat.*, **108**, 726–34 (1952)
46. Zilboorg, G., *Psychoanal. Quart.*, **21**, 1–24 (1953)
47. Freud, S., *A General Introduction to Psychoanalysis* (Liveright Publishing Co., New York, N. Y., 412 pp., 1935)
48. Freud S., *Collected Papers*, **5**, 316 (Hogarth Press, London, England and the Institute of Psychoanalysis, London, England, 396 pp., 1950)
49. Boshe, C. E., *Am. J. Psychiat.*, **108**, 829–34 (1952)
50. Cameron, D. E., *Am. J. Psychiat.*, **109**, 183–87 (1952)
51. Holt, W. L., Jr., and Holt, W. M., *Am. J. Psychiat.*, **108**, 735–39 (1952)
52. Greenblat, M., and Soloman, H. C., *Am. J. Psychiat.*, **109**, 262–65 (1952)
53. Whitty, C. W. M., Duffield, J. E., Tow, P. M., and Cairns, H., *Lancet*, **I**, 475–81 (1952)
54. Petrie, A., *J. Mental Sci.*, **98**, 326–29 (1952)
55. Penfield, W., *Presidential Address Am. Neurol. Assoc.* (Atlantic City, N. J., 1951) *Arch. Neurol. Psychiat.*, **67**, 178–98 (1952)
56. *Group for the Advancement of Psychiatry*, Rept. 1, 1–2 (1947)
57. Rennie, T. A. C., *Ann. Rev. Med.*, **4**, 253–60 (1952)
58. Whitehorn, J. C., *Am. J. Psychiat.*, **110**, 81–83 (1953)
59. Whitehorn, J. C., *Am. J. Psychiat.*, **109**, 81–88 (1952)
60. Lindemann, E., *Am. J. Psychiat.*, **109**, 89–92 (1952)
61. Cameron, N., *Am. J. Psychiat.*, **109**, 93–95 (1952)
62. Levy, D. M., *Am. J. Psychiat.*, **108**, 481–94 (1952)
63. Potter, H. W., and Klein, H., *Am. J. Psychiat.*, **108**, 193–97 (1951)
64. Brosen, H. W., *Am. J. Psychiat.*, **109**, 188–95 (1952)
65. *Group for the Advancement of Psychiatry Report* (In press)
66. Knight, R. P., *J. Am. Psychoanal. Assoc.*, **1**, 197–221 (1953)
67. Warren, S., *Am. Scientist*, **40**, 677–79 (1952)
68. Stevens, N. E., *Am. Scientist*, **37**, 119–21 (1949)

DISEASES OF THE RESPIRATORY SYSTEM

CIRCULATION THROUGH THE LUNG AND DIFFUSION OF GASES[1,2]

By Joseph L. Lilienthal, Jr., and Richard L. Riley[3]

Departments of Environmental Medicine and of Medicine, The Johns Hopkins University, Baltimore, Maryland

It is the intent of this review to take stock of several fields wherein the understanding of physiological and pathological mechanisms appears sufficiently advanced to invite broad application to the interpretation of diseases of the respiratory system. The areas selected by these criteria are the circulation through the lung and the diffusion of respiratory gases. The body of observations, interpretations, and speculations on which are based the concepts of mid-1953 was not formed since the last volume of these *Reviews;* and thus it is hardly profitable to ignore or exclude the investigations reported many years before the period assigned ordinarily to a review of this sort. On the other hand, a catalogue of all the work which well might be relevant to the subjects under scrutiny might dull the interest of the reader, could tax the facilities of the editor and publisher, and surely would exceed the capacities of the authors. Thus, the content of this review will be limited, and within each subject the selection of material may reflect bias which the authors have striven to neutralize. Omission of references to work which seems especially pertinent to the reader will be then the inevitable result of the deepening confusion engendered by the mounting flood of the world literature, if not more likely to be a failure to recognize the significance of tangential or even direct evidence. An attempt has been made to review without limits imposed by continental or linguistic considerations: it is hoped that deficiencies on this score may be understood if they cannot be excused.

The Circulation Through the Lung

Burton has said so aptly, "Few subjects are more confidently discussed by some physiologists without any proper grasp of fundamentals than haemo-

dynamics" (27). This valid censure applies with especial force to some conclusions derived from observations made in man where the opportunity to measure critical forces may be limited sharply.

Nevertheless, the clinician and the physiologist have been developing technics and making measurements in recent years which have clarified our understanding of some of the conditions under which the pulmonary circulation operates. Out of these co-operative and complementary studies has come a firmer realization that an earlier and artificial separation of respiratory from circulatory function was misleading; indeed, the interweaving of these two functions cannot be unraveled under normal conditions, and they become inextricably linked in disease (14, 34, 36, 136). It is for this reason that some special problems of the pulmonary circulation are to be considered here in the light of their relation to the manifestations of disease of the lungs, as well as the pulmonary disturbances consequent to primary disease of the circulation.

The lesser circulation possesses certain extraordinary characteristics which distinguish it from all other special circuits. These unusual features have combined to make experimental measurements extremely difficult to accomplish and to encourage much imaginative speculation, some of which has come to assume the guise of established fact. Certain major features by which the pulmonary circulation differs from the systemic merit re-emphasis: the minute blood flow is that of the output of the right ventricle together with a small but greatly expandable contribution from the left ventricle via the bronchial arteries; the perfusing pressure is approximately one-seventh and the pressure drop across the bed only one-tenth that of the peripheral circulation; the capillaries which traverse the alveolar walls virtually are festooned in a gaseous matrix so that the supporting pressures of adjacent tissue must be very small indeed. The entire cardiac output hurtles through this delicate system, yet even when the minute blood flow approaches that of the contents of a five gallon gasoline can, the delicate balance between oncotic and hydraulic pressures is regulated so exquisitely that gaseous exchange is accomplished without appreciable exudation of fluid.

It was not proposed here to review the hemodynamic principles which govern the circulation through the lung. However, the obstacles in the way of organizing the diffuse material to be considered suddenly fell away when it was realized that these widely diverse topics arranged themselves naturally within the framework of Burton's lucid discussion of the "Laws of Physics and Flow in Blood Vessels" (27). Any paraphrase of his sprightly essay is an act of vandalism; but some listing of the factors and forces which determine circulation will serve best to introduce the work to be considered later.

The laminar flow of simple liquids through nondistensible tubes was described by Poiseuille to obey the following relationship:

$$F = \frac{\Delta P \times \pi r^4}{8\eta l},$$

where F = flow, ΔP = the pressure gradient, r = the cross-sectional diameter, l = length of the system, and η = the viscosity of the liquid.

The simple relationship defined by Poiseuille's law almost certainly does not describe precisely the circumstances of flow and its alteration through a complex vascular net. Nevertheless, the parameters contained in that expression are those on which flow must depend, and it is convenient, therefore, to consider Poiseuille's formulation as a roster of parameters which ought to be examined if the performance of the pulmonary circulation is to be understood. These factors follow.

Flow.—Ordinarily in man it is assumed that this value is equivalent to the cardiac output and that the contribution from bronchial arteries to venous return to the left heart is negligible. The expansion of the bronchial bed or vascular anomalies may make this assumption invalid.

Pressure.—Emphasis must be laid on the fact that it is the pressure gradient which is required, and this, in general, is measured at sites of inflow and outflow. Continued refinement of technics makes it probable that pressure gradients existing within special segments of the circulation may some day be defined, but at the present we know little of these values as they operate, for example, from one end to the other of the alveolar capillary or from the terminal bronchial arteriole to its anastomosis with the pulmonary capillary bed.

Geometry.—The r and l of Poiseuille's equation define the anatomy of the circuit in terms of its cross-sectional diameter and length. It is these same variables which define the volume of the system.

Viscosity.—The requirement that the liquid be simple is not met in the case of blood where viscosity is "anomalous" and varies with the velocity of flow. The observed deviation of pressure-flow relations from the theoretical prediction has been attributed in the past largely to the effect of anomalous viscosity. The same deviations are observed when simple liquids are perfused through a vascular bed so that this explanation has little support, but the possibility remains that in certain pathological states, *e.g.*, erythemia or anemia, the effect of changes in viscosity on pressure-flow relations may indeed become significant. Specific information on this point is lacking.

Laminarity of flow.—Blood flow is essentially laminar within normal vascular channels and thus satisfies one requirement of the Poiseuille formulation; whether turbulence is evoked in diseased or anomalous pulmonary vessels is not established although the production of murmurs suggests that it occurs. To what extent such turbulence may alter circulation is not known.

Distensibility.—This general expression is employed here to incorporate the resultant of a number of interrelated factors: elasticity of the vessel wall, the critical closing pressure, the indirect effects of changes in supporting tissues varying with degree of inflation of lung and intrathoracic pressures, and the direct effects of active vasomotion to the extent to which it may occur. Distensibility, in this sense, is a handy way to avoid using the word "tone," but it is a craven device because the parameters can be equally vague.

Resistance to flow.—This useful expression is simply the ratio of the driving force or pressure gradient to the volume of flow it produces, $R = \Delta P / F$.

Critical closing pressure.—As a result of an entirely new approach to the problem by Burton and his colleagues (26, 27, 143) another important measure of vascular performance has been introduced. This new principle takes into account the diameter of the vessel as the result of the Laplacian equilibrium existing between the pressure of the blood and the tension in the wall. Implicit in the relations described is the instability of the vessels of small diameter which will tend to close down actively and completely if the opposing pressure within them falls to some finite level, the "critical closing pressure." Among the consequences of this feature of small blood vessels the following are of special significance for the circulation through the lung: the critical closing pressure may readily exceed the blood pressure and thus account for closure of vascular channels despite an arterial pressure considered to be adequate for perfusion: the CCP,[3] modified as it is by the intrinsic resistance to deformation of the vessel wall, is altered by vasomotion so that whatever may increase tone in vessel wall may readily obstruct flow completely and so alter profoundly the pressure-flow relations. It is believed that the concept of the CCP well may go far to explain certain hitherto poorly understood features of the pulmonary circuit.

From this résumé of some of the features of circulation, which are presented so clearly by Burton, there emerge certain rigorously defined physical values against which may be set for comparison observations made in the extraordinarily complex system existing in the living organism.

GEOMETRICAL CONSIDERATIONS: SHUNTS AND THE BRONCHIAL CIRCULATION

Although it has long been established that shunting of blood from arteriole to vein occurs commonly in certain special circulations, as for example the finger or the skin, the question concerning the existence of channels which short-circuit the alveolar bed has remained moot (90). The spontaneous development of pulmonary arteriovenous fistulae has suggested the presence of potential underlying communicating pathways, and indirect physiological evidence from normal men made the existence of such shunts a real probability (133). Finally, in patients with advanced pulmonary emphysema the amount of poorly saturated blood which arrives at the left heart is so enormous as to suggest strongly that, in addition to inadequate alveolar ventilation (97), the unsaturation observed is attributable in some undetermined degree to true shunting (16, 60). Prinzmetal and his colleagues introduced the technic of injecting glass spheres of various diameters into circulatory beds to discover whether there were potential shunts and what their size might be (155). They described experiments in living laboratory animals in which glass spheres 10 times the size of pulmonary capillaries were passed in appreciable numbers from the pulmonary artery into the left heart. This same technic has been applied by perfusing the normal human lung, and

spheres up to 0.5 mm. in diameter traversed the pulmonary circuit from right to left (177). Finally, in the dog, Rahn, Stroud & Tobin have seen and photographed visible shunting of thorotrast injected through a catheter wedged into a branch of the pulmonary artery (157). Of considerable interest is their comment that these shunts opened only when the catheter was pressed into the artery, but that, once open, the shunt continued to function after partial withdrawal of the catheter. Recent studies by Gordon *et al.* (96) controvert the impression that arterio-venous shunts exist in the lung. They examined rat and rabbit lungs by a technic of perfusing a fluid immiscible with blood (air, mercury) into the pulmonary artery and determining the pressure required to force the fluid through. By indirect calculation an estimate of the largest caliber vessels between arterial and venous limb can be made. By this method they could find no evidence for communications exceeding 19μ in diameter. The authors expressed their awareness of the unknown factors which might be introduced by the technic; it would seem that judgment might best be suspended because the method does not appear certain enough to negate other positive evidence of shunts, albeit this evidence, too, is not absolutely certain. In addition to probable shunts from pulmonary artery to the venous side, there is accumulating evidence that in disease large anastomoses may appear between the bronchial and pulmonary arteries and that a large arterial supply may flow from the aorta into mediastinal and pleural structures and thence into the pulmonary circulation (31, 139). It would appear now that there is small doubt that large potential shunts of several types exist; the unanswered questions concern the extent of their functioning in health and disease and the degree to which they may expand.

The existence of the bronchial circulation has been known for three centuries (44) and its role long thought to be restricted mainly to subserving the "metabolism of the lung." The rich capillary anastomoses of bronchial with pulmonary circulations have been recognized for a century (140) yet the full effect of this union of systemic and pulmonary beds has been suspected only in recent years (46) and the participation of the bronchial circulation in disease processes only recently studied extensively. Daly and his colleagues are responsible for demonstrating that the maintenance of optimal function in perfused lungs was dependent in part on adequate perfusion of arterial blood via the bronchial arteries (45, 46). It is likely that under normal circumstances the volume of flow through the bronchial arteries is relatively small; Bruner & Schmidt found in the dog that bronchial flow rarely exceeded 1 per cent of cardiac output (25). Nevertheless, this small volume should not be taken to indicate that bronchial flow cannot affect the hemodynamics of the pulmonary circuit; Berry & Daly showed clearly by means of dynamic perfusion experiments that a rise in P_{BA}^2 produced a conparable rise in P_{PA}^2 and F_{PV}^2 (17). The evidence that precapillary anastomoses between bronchial and pulmonary arterial trees are open in normal lungs is conflicting: Miller (140) believed that his anatomical studies belied their presence, and Cudkowicz & Armstrong (42) could not detect perfusate issuing from the pul-

monary arteries when the bronchial arteries were perfused in normal human lungs. On the other hand Marchand, Gilroy & Wilson (139) demonstrated to their satisfaction that appreciable anastomosis did exist in the normal lung. We believe that the weight of positive evidence, both anatomical and physiological, suggests that precapillary anastomoses do exist and that they are likely to be largely potential rather than functional in normal lungs in the resting state. It is likely that the hemodynamic changes needed to open these anastomoses are slight indeed.

No such uncertainty surrounds the problem of the development of anastomoses in disease. There have been a number of important earlier studies on the subject to which reference may be found in the newer reports reviewed here. The New Haven school of Liebow, Lindskog, and their colleagues (131) have recently investigated the bronchial circulation and have demonstrated and emphasized the enormous size to which this bed may grow under the influence of several pathological stresses. Bloomer *et al.* (19) measured by means of bronchospirometry the blood flow through the lung of the dog in which the pulmonary artery was occluded. Immediately after occlusion some gas exchange continued in the lung from which pulmonary arterial flow had been excluded, and over the succeeding weeks blood flow, which must have arisen from the bronchial supply, mounted steadily from an estimated maximum of 30 ml./min. to attain values in excess of 1 l./min./m.[2] and in one instance over 2l. Under these circumstances the output of the left ventricle may be one-third, or more, greater than that of the right heart. Pathological studies of this preparation showed that expansion of the bronchial collateral bed was far advanced in 3 months and that by 10 months there were easily demonstrated precapillary anastomoses exceeding 50μ in diameter (130). At this stage the cross-sectional diameter of the bronchial bed at the level of the sixth order bronchioles was larger than that of the pulmonary artery, which had not thrombosed distal to the ligature.

Recently, improved technics of study by injection, by histological analysis, and by certain physiological measurements have provided some concept of the extraordinary distortions of the bronchial circulation which follow disease of the lung in man. Cudkowicz & Armstrong (43) by means of carefully performed combined injection and histological technics have studied the vascular pattern which characterizes pulmonary emphysema. From earlier studies of normal lungs they had concluded that the bronchial circulation played a paramount role in supplying adequate nutrition to the elastic alveolar matrix (42). In emphysema there was noted extensive narrowing or obliteration of both intra- and extrapulmonary branches of the bronchial arteries as the result of medial hyperplasia and intimal proliferation. Extensive bronchial to pulmonary anastomoses had developed. They believed that there was a significant correlation between the severity of the emphysema and the extensiveness of the vascular obliteration. In those instances where cor pulmonale had supervened there was virtual extinction of the normal bronchial bed and there had appeared profuse anastomotic

connections between the lumina of the pulmonary arteries and their vasa vasorum which were bronchial in origin. These authors discuss at some length the interplay of arterial lesions with the pulmonary disease, and, perhaps wisely indeed, avoid any unsupported speculation concerning the causal relation of these changes. Nevertheless, the implication of these observations makes it possible that primary disease of the bronchial arterial tree might be a beginning defect that leads to emphysema. This possibility gains in attraction when one considers that the supporting structures of the alveolar bed are dependent largely on the bronchial arteries for their blood supply (46). If certain forms of emphysema were the consequence of initial disease in the supporting vasculature then some speculation might be forthcoming in explanation of the patchy, localized, and premature forms of emphysema which occur without other obvious cause. On this principle, Crenshaw & Rowles (40) have reported a surgical approach to the treatment of advanced emphysema in which segmental resection of diseased lung leads, among other things, to an enriched collateral circulation in the remaining lung.

Liebow, Hales & Lindskog (132) and Cockett & Vass (32) have demonstrated clearly in bronchiectasis the prodigious expansion of the bronchial arterial bed and the development of numerous bronchial-to-pulmonary shunts in the diseased portion of the lung. For several years a French school has suggested that bronchial arterial occlusion is the primary pathogenetic process leading to bronchiectasis (1, 128). In the light of the known importance of a proper bronchial arterial supply for support of normal function in pulmonary tissue this proposal has been provocative, although experimental support was lacking. Ellis, Grindlay & Edwards have made a careful study of this question in the dog (76, 77, 78). They have developed ingenious surgical technics for approaching the problem and found that obstruction of a lobar bronchus alone produced no alteration in the bronchial arterial architecture. If occlusion of the bronchial artery were added to bronchial obstruction there followed rapid re-establishment of a normal bronchial arterial pattern; if infection were superadded the bronchial artery supply was expanded greatly. In eight dogs simple bronchial obstruction failed to produce bronchiectasis. One of eight other dogs with occlusion of both bronchus and bronchial artery developed localized bronchiectasis. They concluded that these observations neither excluded nor established the importance of bronchial artery closure in the pathogenesis of bronchiectasis.

The changes in vascular pattern which develop in and around tuberculous lesions have been studied for years. Productive endarteritis is seen commonly in cavity walls and also is widespread in areas of scar and both parenchymatous and peribronchial fibrosis (52). The occlusive process in the pulmonary arterial tree surrounding tuberculous bronchiectatic areas has been demonstrated by angiography (94). Wood & Miller (187) had shown earlier that the dilated, tortuous vascularization in the vicinity of tuberculous lesions was owing to ramifications of the bronchial artery supply. Cudkowicz (41)

has examined tuberculous lungs by means of his combined injection and histological technics. He found not only that there was consistent gross enlargement of the bronchial arteries but that concurrently the pulmonary arteries were thrombosed in these same affected areas. When recanalization occurred it was by way of the vasa vasorum which in turn carried bronchial artery blood. Cavity walls were supplied solely by bronchial arteries and, indeed, there was dilatation of bronchial arteries in the neighborhood of lesions no larger than tubercles. In common with that occurring as a result of mitral stenosis, it would seem that some of the anomalous phenomena associated with hemoptysis occurring in pulmonary tuberculosis might be explained by the fact that bleeding is literally arterial in origin. Furthermore, if it be strictly true that the blood supply to tuberculous lesions originates for the most part from bronchial arteries, then it may be necessary to reconsider many past speculations which have been based on the assumption that the blood supply to the tuberculous area is derived mainly from the pulmonary arterial tree. In view of the extraordinarily deleterious effect on the evolution of a tuberculous process in the lung of the monkey in which an anastomosis has been made surgically between a pulmonary and a systemic artery (107, 149, 172), one may well wonder whether one potent vascular factor in determining the course of the disease may not be the degree to which the normal low pressure venous pulmonary perfusion is supplanted by the higher pressure arterial bronchial supply. That the effect of these changes in the bronchial circulation may well outlast the period of active disease is suggested by the studies of McClement et al. (137) on patients with hematogenous pulmonary tuberculosis in whom a favorable outcome followed treatment with streptomycin. In the "healed" phase, when other measurements indicated that pulmonary function in general was within normal limits, nevertheless, P_{PA} rose during mild exercise. This persistent abnormality is consonant certainly with the probable dilatation of the bronchial bed and its anastomoses likely to have been evoked by so diffuse a process, as well as other changes producing an increased resistance.

The alterations in perfusion pattern accompanying obstructive collapse of a lung or lobe is indicated by the observations of Gilroy et al. (93) who found that blood in the pulmonary artery leading to the nonventilated area was virtually fully arterialized. Subsequent injection studies revealed the probable source of arterial blood to be from the dilated bronchial bed via its anastomoses with the pulmonary arterial bed. From their report it would appear likely but not certain that there was no contribution to the fully oxygenated sample from blood drawn back from the alveolar bed. Steinberg et al. (174) showed by angiography the reduction and delay in the pulmonary artery circulation through a lung collapsed by pneumothorax.

Attention is drawn again to the extraordinary finding of Wood & Miller (187) that the bronchial arteries produced a luxuriant vascular proliferation around primary neoplasms but none about metastatic deposits. These newer findings give sturdy support to Daly's (46) earlier suggestion that the

bronchial circulation might well play a role of special importance in disease. It constitutes a highly reactive auxiliary vascular bed which responds to a variety of disease processes by expanding its volume, and thus may introduce by itself significant changes in pressure and flow relations within the pulmonary circuit.

Volume.—We have reviewed certain features of the geometry of the circulation through the lung (the r and l of the Poiseuille formula) which may be susceptible to change during physiological adaptations and in the course of disease. Together these changes affect the volume of the circuit, and this feature will be considered now. It need hardly be stressed that the structural characteristics alone do not determine the volume of the bed; other determinants such as "distensibility," vasomotion, and the effects of cardiac performance are crucial.

It is worthy of emphasis that the pulmonary circulation "volume" means different things to different persons. When this volume is measured by dyedilution, it may be as large as that which includes the great vessels, cardiac chambers, and arterial bed out to the plane of sampling, and the average volume so measured exceeds 1.1 l. (72). By contrast, the volume of blood which is participating in respiratory gas exchange in the alveolar capillaries at any moment probably is less than 100 ml. (166). Furthermore, as was pointed out earlier, the volume of blood within the lungs proper may be increased enormously by disease processes which result in expansion of the bronchial vascular bed. This distinction in the kinds of volumes which are being discussed is not an idle one; for it is conceivable that large changes in volume may occur in the segments of supply and return to and from the alveolar bed without appreciable change in the contents of pulmonary capillaries, and by the same token the converse might be true. Because the primary function of the pulmonary circulation is to effect an adequate transfer of gases between blood and alveolar air the critical portion of this circuit lies in that segment which traverses the alveolar wall. The evidence for changing volume in this restricted area is circumstantial but attractive for the case of normal man under a work load (158), and the details will be discussed below. The problem of the volume of the whole pulmonary circuit is by no means solved, but there are many recent observations which furnish some definition of the changes in this volume and the circumstances under which these changes occur. The great bulk of this intrapulmonary vascular volume is so closely related to the volume of the heart that it is reasonable to consider the large vessels and the chambers of the heart as reciprocal plenum chambers. The view and the supporting evidence that most of the change in content of blood in the chest is accounted for by changes in cardiac volume have been presented by Hamilton in a delightfully clear review (105). His analysis of certain evidence led him to conclude "that the heart itself acts as a flexible reservoir for blood, acting in large part to cover the function which had been previously attributed to the lungs." For a contrasting view of this complex problem the recent review of Sjöstrand should be consulted (173).

On the basis of experiments on intact man, in whom displacements of blood must be measured by indirect means, Sjöstrand concludes that, in addition to the heart itself, the venous side of the pulmonary circuit constitutes a large reservoir of blood which is readily and rapidly mobilized to furnish an adequate venous return to the left heart when cardiac output rises abruptly in response to, for example, the onset of physical work. In support of these physiological observations he adduces morphological evidence which stresses the large capacity of the venous radicles into which the pulmonary capillaries issue. Indeed, there is circumstantial evidence from this work that the primary reserve blood volume lies within the thorax rather than in the systemic circulation; if this localization is quite true then the effect on cardiac performance produced by any pulmonary disease tending to reduce or to restrict the availability of the pulmonary blood reserve might be manifested in circulatory disability (e.g., response to exercise) before any alteration on the arterial side of the circuit had become detectable or significant.

There is no doubt whatever that the intrapulmonary volume may be swollen or shrunken by dislocation of blood out of and in.o systemic loci (10). An intensive analysis of the manifold effects of various pharmacological agents on the volume of isolated perfused lungs of dogs and cats was made by Gaddum & Holtz (89), and similar careful studies have been made on the effects of other stimuli by Daly and his collaborators (45 to 50). These results will be considered later in detail but have been recalled here to point out that under careful experimental conditions where the isolated lung, separated from the heart, is perfused at either constant flow rate or constant pressure there are situations in which the intrapulmonary volume of blood may vary appreciably.

Recently Sarnoff and his colleagues (167, 169, 170) have been investigating the explosive pulmonary edema which follows on intracisternal injection of fibrin in the dog. They found that this maneuver induced intense peripheral vasoconstriction and arterial hypertension, the basis usually assumed to underlie acute left ventricular failure and, thus, to lead to neurogenic pulmonary edema. However, parallel with the rise in systemic pressures there occurred a moderate rise in P_{PA} and an appreciable rise in P_{LA};[2] flow through the lung fell somewhat and there was no rise in calculated resistance to flow through the lesser circuit. The explanation offered to account for the rise in pulmonary pressures to a level leading to escape of edema fluid was that the volume of the pulmonary tree was increased by a displacement of blood from the periphery. The evidence for this was the absence of increased resistance to flow existing in the lung, the failure of complete pulmonary denervation to block the phenomenon, and finally the direct weighing of a lung lobe *in situ* which gained in weight. Thus, there exists evidence that an expansion of intrapulmonary, as contrasted with intrathoracic, blood volume may alone account for significant rise in pressure throughout the circuit. That such a relation exists is not surprising, but the degree of pressure rise in a system often loosely considered to possess the capacity to be distended passively

requires further analysis. An analysis of this sort has been made by the Sarnoffs & Berglund (168, 169) in both isolated and intact dog lung. The pressure-volume relationship was found to be linear; the volume, measured by weight of lung, rises with increasing P_{LA}. On reducing P_{LA} from elevated levels, however, the volume of the bed does not decrease as rapidly as the pressure and the new relationship is curvilinear with a downward convexity. This phenomenon, stress-relaxation, implies adjustments in the capacity of the pulmonary bed so that large volumes may be accommodated at lower pressures.

Complementary observations have been made in normal man by Doyle *et al.* (64) who measured changes in the central pressures and volumes accompanying the rapid intravenous infusion of physiological saline to the amount of 1 l. in 6 to 12 min. There were sharp rises in central pressures which correlated well with the expansion in total blood volume, but the method employed detected a mean rise in the central volume amounting to only 70 ml. Either the method has insufficient resolution to differentiate volume changes of this order or, perhaps, changes of this small amount are sufficient to elevate pressures in what the authors term the "relatively indistensible pulmonary circuit." Comparable studies were made by Witham, Fleming & Bloom (186) who infused $\frac{1}{2}$ l. of 6 per cent dextran in 20 min. Similar sharp rises in P_{PA} and P_{PC}[2] occurred in conjunction with expansions of total blood volume of the order of 13 per cent. In these studies, however, the calculated central volume increased by as much as one-fifth or more. One important difference between these two studies was that there was no consistent change in cardiac output following saline infusion while dextran infusion, on the other hand, increased output by more than one-third of the average.

Doyle, Lee & Kelly (63) have made an entertaining, highly speculative analysis of their measurements of cardiac output, circulation time, and central blood volume in a large series of subjects comprising various states of cardiovascular status, ranging from normal to failure. Their treatment of these data when compared to that derived from simple physical models suggests that the elasticity of the pulmonary vasculature varies as a function of the quantity of blood flowing through it: at low flows during rest the vascular bed behaves as if it were a simple elastic system, at high flows it mimics a rigid, nondistensible system, and at very low flow rates, the meager data are consonant with a flaccid system with "overstretching and dilatation, of the left heart."

It is fair, we believe, to assume the position that while an encouraging beginning has been made toward an understanding of the phenomena which affect the pulmonary blood volume and the ways by which the pulmonary blood volume may modify other parameters in the circulation, nevertheless, the tools for measuring these several values in the intact animal or man are still inadequate for precise resolution. When Ebert & Borden and their colleagues (22, 72) first reported their study of the central blood volume, some

reservations were expressed concerning their finding that despite the presence of mitral stenosis no enlargement of the central volume was detectable by dye-dilution measurements. On the other hand, the resolution of the method was sufficient to disclose a small increase in central volume accompanying the appearance of acute failure of the left heart. This normal volume, which they found in mitral stenosis, was extremely difficult to reconcile with the familiar pulmonary engorgement which may be demonstrated at autopsy even though no radiological evidence of congestion was adduced during life, as was the case in the patients whom they studied. In the light of newer knowledge regarding the potential contribution of the bronchial circulation, it would appear possible that the discrepancy may be accounted for on the basis that the major increase in intrathoracic blood volume occurs within the bronchial bed. Although it is possible to speculate on how this expanded bed might distort estimates of volume made by dye-dilution technics, there is no experimental evidence on which to base any satisfactory conclusion.

Pressure.—It was emphasized earlier that pressure gradients in a flowing system are inextricably linked to, among other things, its geometry, determined by the cross-sectional diameter and length of the tube through which the liquid flows. This is to say that any definition of flow requires the simultaneous assessment of pressures, geometry, and the other factors which affect flow. Nevertheless, for purposes of discussion these interdependent parameters are forcibly separated and inspected in the familiar fashion required for preliminary analysis of any complex multifactor system. The recurrent danger in any such analysis resides in neglect in the final synthesis of certain important factors which have defied measurement in the experiment. With this disclosure of inherent vice we shall continue with a necessary but dangerous isolation of these factors by considering pressure relations within the pulmonary circulation as though they were unique in affecting flow. A demonstration of what effect systemic pressures may exert is found in the work of Haddy *et al.* (101).

In addition to the difficulties of measuring everything at once, there are serious methodological problems encountered in measuring pressures so as not to introduce disturbances in normal flow. These problems have been attacked serially by devising ingenious experimental procedures which depend on isolation of the pulmonary circuit either *ex* or *in situ* so that one or another variable may be controlled at will. A familiar criticism of this sort of experimental approach implies that information so obtained has little or no bearing on function in the intact man. When the criticism is couched in these unqualified terms it is patently invalid and requires no elaborate answer: the plain fact is that the existence of many of the mechanisms now known to operate in the intact animal were and continue to be uncovered by just such "unphysiological" observations. It is true, however, that what must precede the introduction of such mechanisms into descriptions of function in man is knowledge of the extent to which they may operate in health and disease. The need for the foregoing statements will appear evident in the discussion

to follow, for many of the technics, observations, and concepts have arisen or been tested in relatively isolated preparations.

In man the advent of cardiac catheterization has provided means for recording the P_{PA} and thus the higher pressure of those determining the pressure gradient, $\Delta P = P_{PA} - P_{PV}$ (or P_{LA}), is well defined in a number of circumstances. In man the P_{PA} at rest is of the order of 22 systolic, 8 diastolic, and 14 mean, expressed in mm. Hg, and the variation encountered in normal subjects rarely exceeds 5 mm. Hg above or below these averages (35, 54).

The striking adaptive response of the normal pulmonary circulation to an increased load induced by mild exercise is the maintenance of P_{PA} at a constant level despite appreciable increase in flow, as was shown independently by Hickam & Cargill (117) and by Riley and his associates (161). The exact limits imposed by intrinsic resistance to stretch of the pulmonary bed are not established with respect to the entire range in normal man, but Cournand *et al.* (39) examined this problem in patients after pneumonectomy, and it would appear that as the pulmonary flow through one lung exceeds 5 l./min./m.² body surface a gentle rise in P_{PA} begins to appear. When this figure is projected to that mythical man whose body surface is 1.73 m² then the pulmonary flow through his two lungs which may be accommodated without rise in P_{PA} exceeds 17 l./min. This is probably a justifiable extension in view of the studies of Dexter *et al.* (54) on patients with left-to-right shunts. It is likely that this is a minimal value.

Although clinical judgment of cardiorespiratory performance is aided so often by observing the effect of change in position of the body there are relatively few observations recorded on this matter. Lagerlöf *et al.* (125) have studied the alterations produced on both pulmonary and systemic circulations when a normal subject is tilted, feet down, from the horizontal to 60°. Of interest was the almost immediate fall in P_{PC} and slight fall in P_{PA}. From simultaneous flow measurements it was calculated that resistance to flow rose. When the subject was returned to the horizontal all these changes were reversed.

Both Hickam & Cargill and Riley *et al.* discovered that patients with chronic pulmonary disease of several forms, both emphysematous, fibrotic, and combined, responded to mild exercise with a rise in P_{PA} whether or not the P_{PA} at rest was within the normal range.

Subsequently, several studies have been reported concerning the features of pulmonary hypertension, at rest or in response to work, in a number of primary diseases of the respiratory system (6, 9, 36, 38, 55, 56, 81, 109, 188). Reference to these reports is urged for those who may require detailed measurements; only certain features of these studies will be treated here. It is reasonable to conclude that there is some direct proportionality between the severity of the underlying respiratory disease and the degree of abnormality in the pulmonary circulation; by and large, this must be true, but not infrequently the gage by which we judge the severity of the disease process may turn out to be unreliable. Both Borden *et al.* (23,) and Mounsey *et al.*

(142) have shown that the degree of emphysema as judged clinically and by measurement of the functional residual capacity correlated poorly indeed with the degree of pulmonary hypertension. The latter group of investigators made an interesting series of observations on the appearance of pulmonary hypertension with the development of failure of the right heart and a subsequent return to normal or precongestive levels when cardiac failure subsided. In view of the gloom which hitherto has so often surrounded the development of vascular decompensation secondary to pulmonary disease, the reversibility of this usually ominous accompaniment, pulmonary hypertension, is most encouraging. It is consonant with the findings of Ferrer *et al.* (81) and Harvey and her colleagues (110) which emphasized the reversibility of the vascular crisis occurring in cor pulmonale.

There are, therefore, several careful studies indicated above which establish clearly that in many diverse forms of primary disease of the lung a stereotyped response in the form of pulmonary arterial hypertension is apt to ensue. Although the response is stereotyped, the forces which produce it are probably manifold and must vary from instance to instance. Indeed, on occasions no underlying disease is detectable at all, for in rare circumstances a serious degree of pulmonary arterial hypertension may be encountered in patients who have no evidence of disease of lung or pulmonary vascular bed nor of any disorder of the heart or systemic circulation. This small group has been studied by Dresdale *et al.* (66), and the characteristic clinical manifestation of effort syncope has been described by them and by Dressler (68), while the accompanying hemodynamics were analyzed by Howarth & Lowe (119).

A knowledge of the level of P_{PA} is very useful, but it does not provide the information needed to calculate the pressure gradient across the pulmonary bed. In the experimental animal ΔP is obtained by simultaneous measurement of P_{PA} and P_{PV} or P_{LA} (106). The usual technics employed in cardiac catheterization in normal man do not make the lower pressures available for recording. However, advantage has been taken in a few instances of patent interauricular septum which permitted direct recording of P_{LA} or P_{PV}. Cournand *et al.* (37) made this study first, and their findings have been amplified and extended by Hickam (116), by Calazel *et al.* (28), and by Weissel *et al.* (180). These important observations are limited only by the unknown quantity of how much the potential or actual shunt had altered normal hemodynamics. In those cases where there existed a large left-to-right shunt the application to normal man of the values obtained would be hazardous. In the main, however, the mean pressure gradient from pulmonary artery to left atrium appeared to be of the order of 10 mm. Hg.

In order to secure some approximation of the downstream pressures in the pulmonary circuit, Hellems, Haynes, Dexter and their colleagues (62, 113, 114) developed the method of wedging the cathether into a pulmonary arterial radicle and recording a pressure which they have equated to that existing in the pulmonary "capillary." They reasoned that they were measur-

ing a static pressure approximating that in the pulmonary capillary bed because the values they obtained were only a few mm. Hg higher than that in the left atrium, and because blood withdrawn was fully oxygenated despite hypoxemia of the peripheral arterial circulation, suggesting free communication between the catheter tip and the alveolar capillary bed. It is a pity that the qualifications noted by the originators of this valuable proximate measurement have not always been observed in the course of subsequent enthusiastic use of the technic by many other investigators. The careful studies of Ankeney (2, 3) are recommended especially for a definition of the relation of P_{PC} to other pressures in the circuit. These measurements were made in the dog which must impose certain reservations in direct application to man. Nevertheless, the usefulness of an estimation of P_{PC} is established because of its faithful mirroring of slow changes in P_{LA}. His evidence that fast phasic changes are not reflected back from the atrium is impressive, and there is good support for the conclusion that P_{PA} is not impressed on P_{PC} in the normal animal. Whether in such instances as mitral stenosis a distended circulation provides quite different relationships is not established. By contrast, Haddy et al. (99) found in normal dogs, as well as those with experimentally induced mitral stenosis, that the correlation of P_{PC} with P_{PV} was very poor indeed, until the P_{PC} exceeded 17 mm. Hg.

The necessity is apparent for critical examination of conclusions based on measurements of the pressure gradient in which P_{PC} is used. Estimation of ΔP from P_{PC} can never supplant direct measurement of P_{PV} or P_{LA}, but if the data are incorporated into the analysis with due care many useful first approximations may be made.[4]

A study of the nature of the interplay of P_{PC} with P_{PA} and pulmonary blood flow has been made by Dexter et al. (54) and by Eliasch et al. (75, 126) in normal men and in patients with cardiac disorders. They suggest that the abrupt rise in P_{PA} and pulmonary resistance that occurs in mitral stenosis as P_{PC} exceeds 25 mm. Hg is a compensatory mechanism to protect the alveolar bed from perfusion pressures exceeding the oncotic pressure of the plasma. Again it is likely that the relation of P_{PA} to P_{PC} is not a simple one, for Araujo & Lukas (4) found in their studies that it appeared that more protection was afforded by reduction in flow than by rise in arteriolar resistance, and that during exercise the P_{PC} rose abruptly without the occurrence of any protective increase in resistance. These two interpretations are not necessarily contradictory. The unyielding resistance in these instances results from the reduction in diameter of the mitral orifice. With the lower end of the pressure gradient thus fixed by geometrical changes, flow can be maintained or increased only by a proportionate rise in the perfusing pressure.

[4] Epps, R. G., and Adler, R. H. [*Brit. Heart J.*, **15**, 298–304 (July, 1953)] have recently demonstrated a remarkable congruence in systolic, diastolic, and mean pressures, as well as venous pulse waves recorded consecutively from a catheter wedged in a pulmonary artery and from a needle introduced through a bronchoscope into the left atrium of seven patients with various forms of mitral valvular disease.

And conversely, if this perfusing pressure is not to rise to levels which may embarrass the right ventricle, then flow must fall. In effect, then, the protection afforded the alveolar capillary must result from an appropriate balance of pressure and flow, and the interrelations of these two will be a variable reciprocal.

Resistance to flow.—The special usefulness of the concept of resistance to flow resides in its simplicity: it relates as a plain ratio the pressure gradient to the amount of resulting flow. But, as is so often true in the case of distilled generalizations, the complexity of the interrelations of the many forces which enter into the summed factors may disappear from view. Consider the patient with obliterative lung disease in whom pulmonary arterial hypertension results from extensive reduction in cross-sectional diameter of his pulmonary arterial vasculature: if cardiac output is maintained the calculated resistance to flow is increased enormously. By contrast, the patient with mitral stenosis or failure of the left ventricle may display an equal rise in P_{PA} proportional, in this case, to the amount of rise in P_{LA}: if flow through the pulmonary artery remains normal no change in resistance has occurred in this instance. It becomes essential first, then, to know where the change in resistance occurs; and subsequently one may attempt the analysis of what alterations have produced the change which has occurred. The pulmonary changes leading to increased resistance which are easiest to imagine are obliterations of the vascular bed which follow intravascular embolization and thrombosis, and fibrotic and inflammatory disease of the lungs. But attractive as these structural changes may be for the purpose of concrete imagery, there are many warnings against embracing this explanation no matter how reasonable it may seem. The original observations of Tigerstedt (176) that acute closure of a main branch of the pulmonary artery did not produce any rise in pressure gave early indication of how much obstruction might be accommodated, and there have been several careful quantitative extensions of this principle (91). McKeown (138) has pointed out that right ventricular hypertrophy occurs in emphysema with and without lesions of small pulmonary arteries; and, further, she found no greater incidence of these vascular lesions in patients dying with pulmonary emphysema than occurred in the control group of similar age. It is not intended to imply here that obstructive lesions do not play a role in the development of heightened resistance to flow; it is hoped, however, to emphasize that compensatory adjustments may negate entirely certain anticipated effects of the vascular obliteration. An instructive and unusual occurrence was described by Edwards & Burchell (73) in the case of a young woman in whom an inflammatory mass had obstructed the pulmonary veins in four of five lobes. There was intense general pulmonary arterial hypertension and severe arterial disease in the four obstructed lobes; the remaining lobe contained a normal vascular tree. This isolated experiment of nature draws attention to the converse effect, the structural vascular response to a rise in pressure. But again, the presence of well marked organic vascular change does not always lead to the expected functional disorder

as exemplified by the findings of Ellis *et al.* (79) where in a series of patients with mitral stenosis all those who developed acute pulmonary edema had pulmonary vascular changes, but so did others in whom edema did not supervene.

Resistance to flow is determined by the pressure gradient operating across the system and the geometry of the bed. The simplicity of this relation, however, is complicated by the fact that the tubes through which the flow occurs are not rigid. This characteristic introduces the complicating factors of resistance of the wall to deformation, a property which may be altered by the amount of external pressure applied to the vessel. An indirect analysis of this factor has been made by Haddy & Campbell (100) in dogs in which mean P_{PV} was raised by the interposition of airway resistances. They found that as P_{PV} rose, relative to a mean intrathoracic pressure of zero, resistance through the pulmonary bed fell, suggesting that the pressure distension of the bed was "an important factor in determining the resistance to blood flow."

The influence of the elastic and viscous properties of the lung itself on the pulmonary vascular bed and its resistance to flow was measured by Nisell (147, 148) who demonstrated that there was a basis for the intuitive speculation that as the elastance of the lung was increased, resistance to flow was altered in the same direction. Edwards (74) recently has reexamined the old problem of what effect on resistance to flow was produced by positive and negative pressure inflation of the lung.[5] The applicability of his studies to intact man is not established because the experiments were carried out in open-chest procedures in dogs, but it is reasonable to assume that several of the principles which emerged apply generally. Inflation led to a significant rise in resistance: for example, a mean P_{PA} of 15 mm. Hg forced 125 ml./min. of blood through the deflated lobe and only 25 ml./min. through the inflated lobe.

Deuchar & Knebel (53) have analyzed data they obtained from cardiac catheterization of patients with the aim of differentiating the contribution to resistance made by the usual peripheral factors from that which results from "elasticity" resistance. This part of resistance arises as a function of the "Windkessel" properties of circulatory beds, the capacity to store potential energy. In patients with primary pulmonary hypertension it was calculated that the peripheral rather than the elasticity factor was responsible for the rise in resistance.

From these various observations it becomes clear that while the expression "resistance" may be an exceedingly useful measure of the sum of influences operating within and upon the pulmonary vascular bed, nevertheless

---

[5] A recent review [Rodbard, S., *Am. J. Med.*, **15**, 356–67 (Sept., 1953)] adduces much evidence in support of the thesis that bronchomotion is an important agency in control of the pulmonary circulation. It is likely that changes in bronchiolar tonus do play a significant role, but evidence is meager or nonexistent to support the suggestion that a differential increase in intraalveolar pressure is responsible for compression of the pulmonary capillaries.

it is hazardous to attribute any change to one or another factor unless all have been taken into account. In the experimental animal this accounting is difficult enough; in man it is frequently impossible to accomplish.

CONTROL OF THE PULMONARY CIRCULATION

There is in historical perspective a recurrent pattern in the development of concepts concerning special circulations. In the earlier stages of investigation the experimental technics available for isolation and measurement of the circuit under study are relatively crude, and unwitting damage is done to the controlling mechanisms. During this period the conclusion is ofttimes drawn that the special circulation mirrors in a passive way the pressures and flows impressed on it by the systemic circulation. With progressive refinement of experimental technics there begin to appear observations which suggest that active vasomotion does occur in response to a host of neural and chemical stimuli. The growth of our knowledge concerning the cerebral and the hepatic circulations are examples of this pattern. For many years this same question has confronted students of the pulmonary circulation, and to this day the dilemma has not been resolved with any finality. There continue to appear reports of meticulous experiments which lead to the conclusion that the pulmonary circulation is in effect an inert reflection of the performance of the heart, but on the other hand there is a weighty mass of data which have been interpreted to establish beyond reasonable doubt that there exist locally within the pulmonary vascular tree effective mechanisms to alter the resistance to flow and thus to control in some measure the flow through that bed. Our concern here is to review the evidence which leads to some judgment concerning the existence of these controls, and further to attempt some assessment of the extent to which they may operate in health and disease.

In a delightful essay which treats of "The Chance that a Phenomenon Has a Significance" Barcroft (13) has said,

Among the phenomena which have been alleged to have no significance is the neuromuscular armament of the pulmonary arterioles. The matter has never been stated precisely in that way so far as I know. Nevertheless, the persistent denials of vasomotor effects in the lung really amount to a plea for a phenomenon without a significance. No one denies either that the pulmonary arterioles possess muscular walls or that these walls possess nerve endings.

For some notion of how profuse is the innervation of pulmonary vessels one may consult with profit the illustrations of Larsell & Dow (127).

Receptor mechanisms.—The complete picture of any circulatory bed which may be thought to respond in independent fashion would require some evidence of receptor activity within the bed itself. Clinically and experimentally, the impression long has been strong that much of the vascular disturbance provoked by embolization of the pulmonary tree could be explained best by a barrage of afferent stimuli arising in the plugged vessels. Whitteridge (184) has reviewed this aspect in detail. Attention may be drawn here to the ear-

lier work of Churchill & Cope (30) and of Schwiegk (171) who demonstrated so clearly that alterations in static pressures within the pulmonary bed produced bradycardia and systemic arterial hypotension, reflexes dependent on integrity of vagi. The finer detail of these receptor mechanisms has been examined more recently by Pearce & Whitteridge (152). By skilful recording from single fibers they uncovered afferent impulses which were discharged in synchrony with the pulse wave of the pulmonary artery and out of phase with the aortic wave. This provided more direct evidence that pressoreceptors were operating on the arterial side of the pulmonary circuit. Aviado *et al.* (8) have concluded recently that the receptive zone on the arterial side is restricted to the first part of the pulmonary artery. They confirmed the earlier observations of Daly *et al.* (50) that the pulmonary veins were well supplied with sensitive pressoreceptors.

Thus there is ample support for the view that pressure changes in the pulmonary bed are monitored locally and that information is transmitted centrally with compensatory reflex adjustments occurring in the pulmonary and systemic circulations (51, 151). Viar & Harrison (178) have described a group of six patients who developed angina pectoris of familiar clinical characteristics except that it was associated with cough of long-standing, cyanosis, unusual dyspnea, and accentuation of the pain with breathing. These patients enjoyed great relief when oxygen was administered but no benefit from nitroglycerine. At autopsy, in several cases, no disease of the coronary vessels or myocardium was disclosed. Each had hypertrophy of the right ventricle and dilatation of the pulmonary artery so that pulmonary arterial hypertension was likely to have been a common denominator. They interpreted the angina to have resulted from sudden distension of the pulmonary arteries as a result of rise in P_{PA} during exercise or excitement with impulses travelling centrally along paths shared in common with afferents from the myocardium. These interesting observations and speculations furnish additional support for the belief that the pulmonary arterial bed may be more sensitive to pressure changes than is ordinarily held, and may offer some partial explanation of certain peculiar pains in the chest which sometimes accompany pulmonary disease.

Effector patterns.—Having established the likelihood that the pulmonary bed is an effective receptive area, we may return to the problem of what and how responses may be evoked in the bed itself. In 1871 Brown-Sequard reported observations, the earliest of which we are aware, that manipulations of central neural structures produced changes which he concluded to be the result of activity in vasomotor nerves travelling to the lungs via the thoracic sympathetic chain. Five years later Lichtheim showed that during asphyxia a rise in P_{PA} might occur without any rise in systemic arterial pressure and deduced that this indicated active vasomotion. In 1894 Bradford & Dean (24) published the results of an extensive investigation of the pulmonary circulation in dogs. This work, which is an exemplar for its or subsequent eras, is recommended highly for study and especially by anyone who believes

that his ideas or questions about the lesser circuit are entirely new. By simultaneous measurement of P_{PA}, P_{PV}, and P_S^2 during stimulation of various segments of the neural inflow to the lung, Bradford & Dean showed the comparative independence of the pulmonary from the systemic circulation, while at the same time they were fully aware of the effects produced by changes in the intraventricular pressure of the left heart. Concerning the efficacy of the controlling mechanisms they concluded that vasomotion in the lung was small and "but poorly developed compared to the elaborate vasomotor system of the greater circulation. It is one thing however to hold the opinion that the pulmonary vasomotor mechanism is comparatively feeble and another to deny its existence. . . ." Barcroft (13) has discussed the evidence obtained by comparative physiologists which demonstrated how general is the mechanism for neural control of pulmonary hemodynamics.

In ensuing years interest in this field died away except for the orderly progression of experiments carried out by Daly and his colleagues (45 to 50). These studies were accomplished initially in sharply isolated preparations, but with steady technical advances their most recent work has been carried on in virtually intact animals. The evidence appears convincing now that in the dog both vasoconstrictor and, to a lesser extent, vasodilator effects may be produced by stimulation of both sympathetic and vagal supply, with significant and appropriate changes in pressure gradient, flow, resistance to flow, and volume of the circuit.

Neurohumoral and pharmacological agents.—If, as has been shown, there exist effective means for controlling the flow of blood through the pulmonary circulation within the circuit itself, the next question, then, is the nature of the stimuli which may evoke a local response and the extent to which they may operate both in health and disease. The original observations of Bradford & Dean preceded by a few years the availability of epinephrine and was followed naturally enough by studies of the effect of this neurohumoral agent on pulmonary hemodynamics. Observations were reported to support and to deny the possession by epinephrine of a capacity to affect the pulmonary circulation. The complexity of the problem was compounded by what are known now to have been important confusing factors, such as the maintenance of adequate bronchial artery perfusion and constrictor substances developing in defibrinated blood. Nevertheless, a study by Gaddum & Holtz (89) provided certain basic information about the reactivity of the pulmonary bed to biological agents. In this investigation, perfusion pressure or perfusion volume was maintained constant alternately and the volume of the lung recorded simultaneously. By this device some estimate was gained of the site of predominant vasomotion, for if during constant volume perfusion the P_{PA} rose and the volume of the circuit fell, then the major constriction had occurred in arterial or capillary bed. If, when the P_{PA} rose, the volume also increased then the site of vasoconstriction was likely to have been in the venous limb of the circuit. In dogs epinephrine produced constriction of the inflow segment, and the effect was reversed after treatment with ergotoxine. The effect on outflow tone was variable. This effect of epinephrine could not

be concluded to have demonstrated a constant direction of action because, by contrast, in the lungs of cats it produced vasodilatation of both arterial and venous beds. This striking species difference echoes the old warning about applying to man the observations made in an experimental animal. But even more it emphasizes the fact that the assessment of the action of an agent with wide-spread effects of opposing directions is fraught with difficulties when the over-all effect is the gage of action. This obstacle to clear-cut decision recurs throughout most of the work to be considered below. It does not constitute a reflection on the skill or sagacity of the investigators but rather highlights the complexity of the system under study. For an immediate example of diametrical opposing results and interpretations the work of Hamilton, Woodbury & Vogt (106) should be consulted. They found in the anesthetized intact dog that large doses of epinephrine produced no change at all in ΔP across the pulmonary bed although the P_{PA} and P_{PV} rose appreciably. And to complete the chronological story of the conflicting studies, more recently Edwards (74) has found a small but indubitable increase in resistance to flow through a partially isolated lobe of the dog after epinephrine.

In man, Goldenberg and his colleagues (95) found that both epinephrine and norepinephrine produced a rise in P_{PA}, but that the two together resulted in a barely significant fall. The basis for the rise was not determinable in these experiments. Somewhat similar findings have been described by Zimmerman (190). Two studies of this problem in man have been reported with estimates of the ΔP by simultaneous measurement of P_{PA} and P_{PC}. Fowler *et al.* (87) examined the circulatory responses to norepinephrine. They also found that P_{PA} rose, but in addition the P_{PC} rose by an equal amount so that ΔP and resistance was not altered significantly. One of the criteria by which these authors gaged satisfactory P_{PC} measurements was the recording of rapid phasic waves, and Ankeney has made the point that under such circumstances in the dog transmission of pressure in the pulmonary artery had occurred around the catheter wall. In view of this newer information, therefore, some doubt may be entertained as to whether or not a rise in P_{PC} had in fact occurred. Witham & Fleming (185) have made a similar sort of study on the effect of epinephrine in man. In five instances they were able to record both P_{PA} and P_{PC} after administration of epinephrine: P_{PA} rose appreciably and P_{PC} rose but slightly. In three of these patients in whom resting P_{PA} was normal the epinephrine injection was followed by a rise in resistance to flow; in the two others with more advanced disease of the lung and an elevated P_{PA} at rest, the pulmonary vascular resistance fell. With admirable restraint the authors concluded that "it could not be demonstrated that the effects [of epinephrine] were due to a direct action of the drug on the pulmonary vascular tree and the mechanism of this phenomenon remains obscure." In view of their measurements of cardiac output, central pulmonary volume, and circulation times performed in the same experiments one may wonder a little at their reluctance to conclude that epinephrine did indeed exert an action on the pulmonary vasculature.

The evidence from experiments by Gaddum & Holtz (89) indicates that

acetylcholine and histamine also may produce profound effects on the flow of blood through the lungs.

In recent years the emergence of agents which block the action of naturally occurring neurohumors has provided a refined but occasionally uncertain tool for uncovering the site and degree of action of several such transmitter substances. The uncertainty arises from the fact that most if not all such blocking agents exhibit a spectrum of actions, rarely if ever localized solely to one effector target. Nevertheless, valuable clues may arise from their use in analysis of function.

Fowler et al. (85) examined the effect of tetraethylammonium (TEA) on P_{PA}, P_{PC}, and the calculated resistance to flow. In three normal subjects TEA had no significant effect. In four of six patients with pulmonary hypertension of moderate degree there was an appreciable fall in resistance to flow. Greene & Bunnell (98) studied the response of P_{PA} to sudden release of increased intrathoracic pressure (Valsalva maneuver) when an "overshoot" occurs. This "overshoot," which has been thought to result in the periphery from an actively constricted arterial tree, is abolished by TEA,[2] which also produced a fall in P_{PA} before the Valsalva maneuver. Dresdale et al. (66) discovered that TEA lowered in moderate degree the pulmonary resistance in the patient with primary pulmonary hypertension, whereas priscoline reduced the resistance to less than one-sixth of its prior value. Frisk et al. (88) record a fall in mean P_{PA} from 13 (23/9) to 8 (14/4) mm. Hg after administration of TEA to a patient with arterial hypertension; they attribute this fall to shift of blood from lesser to systemic beds. Halmágyi and his colleagues (103, 104) have observed changes in P_{PA} and cardiac output and made estimates of the resistance through the lung. There is, of course, the usual reservation when ΔP is not known but, nevertheless, certain interesting events were recorded. The pulmonary hypertension accompanying heart failure was reduced by both TEA and N-(2-chloroethyl) dibenzylamine (Dibenamine). Of especial interest was the fact that when patients with pulmonary hypertension attributed to mitral stenosis or left heart failure went to sleep, the P_{PA} dropped appreciably, and returned to prior levels when they awakened. They found that dihydroergotamine produced significant rise in P_{PA} which was reversed promptly by sodium nitrite in amounts so small that no peripheral pressure changes occurred. The mild hypertension induced by dihydroergotamine was not blocked by TEA. Werkö & Lagerlöf (182) report that theophylline effected a transient but appreciable fall in P_{PA} and P_{PC} of patients with hypertension; there was no accompanying consistent change in resistance.

Another new autonomic ganglionic blocking agent, hexamethonium, has been examined for its effects on pulmonary hemodynamics, and the results are contradictory. Werkö et al. (181) found in patients with systemic arterial hypertension that although P_{PA} fell so did P_{PC}, and the changes in resistance were not consistent in direction. They believed no direct effect on pulmonary vessels was demonstrable but that the changes were attributable to the meas-

ured reduction in intrathoracic blood volume and in cardiac output consequent on systemic pooling of blood. On the other hand, Gilmore and his associates (92) found that P_{PA} fell without any change in cardiac output. They surmised from the extent of the fall that it was unlikely to have been a reflection of a fall of so great a degree in the left heart pressure. After hexamethonium, tilting of the subject resulted in an increase in cardiopulmonary blood volume, a reversal of the usual effect. These authors interpreted their observations to imply "that the pulmonary vessels have a vasoconstrictor nervous mechanism which is blocked by hexamethonium compounds."

Much of this work on assessing the effects of various agents on pulmonary circulation is in an early phase where definitive answers are difficult to reach because technics lag behind the questions which are posed. Nevertheless, the information which is available would appear to make reasonable the following tentative position: the pulmonary circulation possesses the capacity to respond briskly to a number of biological substances and to their blocking agents. In normal subjects in the resting state the responses are slight in most instances. In disease or under stress, however, when the equilibrium state of the circulation is displaced, then the effect of these pharmacological agents becomes more impressive. Sufficient measurements have been made to support the conclusion that these effects are not solely a reflection of hemodynamic changes in the heart and systemic circulation and to suggest strongly that these local mechanisms are likely to assume increasing importance as part of compensatory adjustments to the stress of work and disease.

Respiratory gases.—A rather general physiological principle concerns the responses of an organ system which appear purposive in the sense that the direction in which they go serves best the efficient operation of the system and the needs of the whole organism. On this principle the lungs, which furnish the site for exchange of respiratory gases between the environment and the circulation, might be expected to adjust ventilation-perfusion relations in such a fashion as to preserve an optimum ratio. One manner of making such an adjustment would be to reduce alveolar perfusion through a segment of the lung in which alveolar ventilation was diminished. A direct gage of the degree of alveolar ventilation would be the composition of the alveolar air: for example, if oxygen tension fell in an area, a suitable adjustment would be the exclusion of perfusion to that area. Some such relation must exist to account for the absence of significant venous admixture appearing in the arterial blood during periods of minimal ventilation in the healthy subject and when ventilation is reduced or stopped in appreciable segments of the lungs in disease.

The ventilatory adjustments to changes in the composition of inspired air have been the subject of many investigations over a long period of time; only more recently have the adjustments in perfusion been examined.

It had been long known from the work of Lichtheim and of Bradford & Dean (24) that asphyxia resulted in hemodynamic changes in the pulmonary circulation independent of the alterations produced in the systemic bed. A

modern renewal of interest began in 1946 when von Euler & Liljestrand (80) described experiments carried on in cats with closed chests and voluntary respirations in which the reduction by one-half of the normal oyxgen tension of inspired air produced a rapid rise in P_{PA} which was sustained for the period of hypoxia. Conversely, breathing a high concentration of oxygen lowered P_{PA} below the level recorded when the animal was supplied with room air. They noted, also, as had Binet & Bourliere (18) earlier, that a carbon dioxide content of 6.5 per cent in inspired air was followed by a similar but less extensive rise. In this study they report inconsistent effects following administration of epinephrine, but norepinephrine induced phasic rises and falls in P_{PA} and acetylcholine relaxed the bed. From these observations they drew the conclusion that the local vascular bed was responsive to changing tensions of O_2 and CO_2 and that the response would tend to shunt blood away from the alveolar area impoverished with respect to O_2 or contaminated with excess CO_2. In a subsequent review Liljestrand (134) marshalled the evidence which he believed especially convincing in support of the conclusion that such control of perfusion was a local phenomenon. First, the rise in P_{PA} was not accompanied by any change in P_{LA}; and second, ergotamine increased the ΔP, $(P_{PA} - P_{LA})$, several fold, an effect not attributable to simple distension of the bed because the change was 10 times that induced by sudden occlusion of a main branch of the pulmonary artery. However, the recording of large phasic changes in mean P_{PA} when the systemic pressure was constant, suggested that some vasomotor rhythm had been impressed from central neural structures on a local mechanism. Extensions of these general observations were made by Logaras (135) who showed further that a variety of autonomic agents (dihydroergotamine, atropine, etc.) did not prevent the response to low oxygen tensions although ergotamine reversed the effect of CO_2. The reasonable tentative conclusion at which he arrived was that the effect was largely local. In addition, Logaras was able to make a rough estimate of the prepotency of the local oxygen response by showing that the mild pulmonary hypertension resulting from an increase in inspiratory or expiratory resistance was reduced by oxygen inhalation. This observation provides ground for speculation concerning a partial explanation of the occasional dramatic effect of high oxygen administration in patients with respiratory obstruction.

In the intervening years a large number of studies have been made of this interesting adaptive phenomenon. It is planned to survey first the experiments which have been carried out in the experimental animal before proceeding to those accomplished in man in health and disease. A series of refined but complicated analyses have been made by Nisell (144 to 148); from the mass of data which he has accumulated we have selected arbitrarily certain points of especial relevance to this review. In the lung of the cat perfused *in situ* at a constant volume rate the introduction of hypoxemic or hypercapnic blood into the system produced a fall in the pulmonary resistance. It seemed this occurrence fitted best with the hypoxic rise in P_{PA} in the intact

animal by assuming that the site of vasoconstriction is downstream, i.e., in the venular or venous limb. This conclusion was supported by finding in his particular preparation that as P_{PA} rose, P_{PV} fell. He extended the concept of the mechanisms by which alveolar gas tensions might affect pulmonary hemodynamics by studying simultaneously both the circulatory and ventilatory functions. When the elastic and viscous properties of the lung structure were altered, an accompanying change occurred in the pulmonary bed: as elastance and viscance were increased (less distensibility) the outflow of the lung circuit was restricted, and changes in gas tensions brought about changes in these properties of the lung.

In more isolated lung preparations Hebb & Nimmo-Smith (112) recorded brisk rises of the order to 5 to 7 mm. Hg in P_{PA} in monkeys when high concentrations of CO_2 (20 to 30 per cent) entered the alveoli. Bean *et al.* (15) have demonstrated the complexity of the pulmonary vascular responses to increased CO_2. Duke studied this problem in isolated and perfused lungs of cats and dogs (69, 70), and demonstrated that under the conditions of her experiments there were restrictive vascular responses to increased CO_2 or decreased CO_2 in the ventilating gases. More recently Duke & Killick (71) have continued these observations with isolated cat lung perfused and ventilated *in situ* at a constant volume rate. As before, dilution of inspired oxygen by the inert gases such as nitrogen, neon, or helium, resulted in a rise in P_{PA}. To their surprise carbon monoxide inhalation resulted in a prompt fall in P_{PA}, which could not be attributed simply to anoxia because perfusion of the system with blood containing 80 per cent carboxyhemoglobin did not alter P_{PA}. They suggest that the effect of CO might be the result of its interference with some intracellular respiratory pigment necessary for the maintained integrity of the hypoxic response. This suggestion is consonant with their finding that cyanide and azide, potent poisons for respiratory pigments, also reduced P_{PA}. These observations are of interest in suggesting certain local metabolic processes which might be involved in the perfusion response to changes in ventilation. An important example from another circulation of the extraordinary independence of local vascular responses from central control has been shown clearly by Hilton (118), who demonstrated that full hyperemia of muscle after contraction is developed after all mechanisms save an axone reflex have been blocked.

Some of the earlier work in this phase was carried on by Dirken & Heemstra (57, 58, 59) who developed a somewhat different method of tackling the question. They used rabbits, supplying one lung with air poor in O_2, the other rich. At the outset the oxyhemoglobin saturation of the systemic arterial blood was diminished, but during the course of about 8 hr. the saturation rose virtually to normal levels. They interpreted this compensation to have resulted from slow development of increased resistance to flow through the hypoxic lung. On returning the lungs to 21 per cent O_2 the resistance fell to normal in the previously hypoxic lung in some 4 to 5 hr. They were able to detect a rise in resistance after only a slight reduction in inspired O_2 from

21 to 19 per cent. When CO_2 was added to the gas ventilating one lung a brief and transient rise in resistance followed. In an attempt to isolate the neural pathways involved they resected the sympathetic chain with a resulting increased flow; vagotomy had no effect. Of considerable interest was their finding that at the close of an experiment the hypoxic lung contained 50 per cent more histamine than did the oxygenated lung. This technic of matching one lung against the other provided a real advance in method as applied to this problem because it made it possible to minimize or exclude systemic changes introduced during hypoxia and furnished an admirable control in the same animal. The slow time course of the response in rabbits is puzzling; on teleological grounds alone it is inappropriate, and the explanation is not clear. In view of subsequent findings in other species, it may be that this represents simply another example of the bizarre physiological patterns which are found so often in rabbits; it may be said with some justification that if it is necessary to observe great caution in transferring findings in the laboratory animal to man, then perhaps one should never transfer results in the rabbit to any other species.

Atwell *et al.* (5) used a bronchospirometric technic to rebreathe one lung in the dog so that alveolar gas tensions came into equilibrium with those in mixed venous blood. Three of the six dogs shunted appreciable amounts of blood flow away from the hypoxic lung and P_{PA} rose in four of the five in which this was measured. The time course of this response was something less than 20 min. Peters & Roos (153) examined the effect of supplying gas mixtures with very low tension of O_2 to one lung in the dog. In 8 of 11 dogs the resistance to flow through the hypoxic lung had increased from 1.3 to 4.5 times and the effect was maximal within 25 min. In an interesting duplication of a clinical phenomenon Peters & Roos (154) measured the effect on flow through a lung in which atelectasis followed obstruction of a bronchus. The bronchus was occluded acutely while the dog was breathing pure O_2; the lung was completely collapsed in some 5 min. and simultaneously resistance to flow rose sharply as blood flow was reduced. This reduction in blood flow was maintained chronically.

Rahn & Bahnson (156) reported in preliminary studies that by supplying nitrogen to the left lung in the dog, flow through it was reduced from 45 to 25 per cent of total pulmonary flow and that this reduction began within 1 to 3 min. and attained maximum value in 10 min. In a masterful extension of these studies Stroud & Rahn (175) have reported recently on a more detailed analysis of this phenomenon. In anesthetized dogs they measured P_{PA}, P_{PV}, and cardiac output as well as ventilatory functions when both lungs were supplied with various gas mixtures. With due care for the transient changes that might appear during the unsteady state they recorded the responses during 10 min. periods of inhalation of gases of either enriched or decreased O_2 tension. As the percentage of O_2 was reduced from 21 to 15 to 8 there was a slight rise in cardiac output, an appreciable rise in P_{PA}, and no significant change in P_{PV}. There was no doubt but that resistance had in-

creased; what was particularly clear was that this response was graded and became more evident with increasing degrees of hypoxia. Any changes associated with inhalation of 30 per cent O_2 or 5 per cent CO_2 were equivocal. In three dogs the experiments were repeated after extensive thoracic sympathectomy, and the prior responsiveness had vanished. The effect of pentobarbital anesthesia was well illustrated in that when the P_{PA} and cardiac output were measured in the waking dog the pulmonary hypertensive response was double that encountered during anesthesia. In this case it could not be established beyond doubt that more vasoconstriction had occurred but this was the most likely basis. This blunting of the waking response by barbiturates is reminiscent of the effect of sleeping on pulmonary hypertension reported by Halmágyi et al. (103). There was positive evidence that the vascular response could not be attributed to other mechanical or ventilatory factors.

This careful study of the hypoxic response in the intact dog would appear at the date of writing to describe accurately the over-all phenomenon. That other reactions may occur and, perhaps, be swamped in the predominating pattern is indicated by the experiments of Aviado et al. (7) in dogs where more isolation and control of circulation through a lung was accomplished. These investigators concluded that hypoxia leads to local dilatation and that the rise in P_{PA} was attributable to increased flow and volume and not to contrictor responses. A possible explanation of these differences well may lie in the different experimental design, but the findings are important in that they demonstrate that, in keeping with other vascular beds, the pulmonary vessels are subject to dilator as well as constrictor influences as a result of hypoxia.

Hürlimann & Wiggers (120) showed that steadily progressing hypoxia induced a congruent rise in pressures and flows through the lung and concluded that the major contribution was furnished by the heightened flow rather than the rise in resistance. A companion paper by Hall (102) is remarkable for its neat in situ isolation of a lobe from external influences reaching it from the central nervous system or the bronchial arterial supply. In such a lobe, perfused at various constant pressures via a carotid artery and ventilated at a constant rate and volume, he observed the effect on flow when the lobe was ventilated with nitrogen instead of room air. The displacement of the pressure-flow curve demonstrated that an increase in resistance had occurred and that it became greater the higher the perfusing pressure. Because the blood flowing through the arteriolar bed was fully oxygenated (arising from the carotid) the site of action of hypoxia must have been at the alveolar capillary stage or downstream. This confirms Nisell's (146, 148) conclusion that resistance was built up beyond the capillary bed although Hall is unwilling "to assign the changes definitely to venomotor actions." It may be noted here that there are clear indications that vasoconstriction is not restricted to the postarteriolar segments in other circumstances.

It is at once apparent that although segmental restriction of pulmonary flow will serve a valuable function in trimming perfusion to balance alveolar ventilation, nevertheless, the requirements of the pulmonary circuit are quite different from, for example, the circulation to a finger where virtually complete closure might be tolerated in the face of a cold stress. This is to say that there must be a ceiling to the amount of resistance imposed by the lung if the total circulation is to continue. Under severe stress, therefore, one might expect that "the call for oxygen" by body tissues might override the restrictive response. Lewis & Gorlin (129) have studied the effect of profound hypoxemia in dogs where pressures and flows were measured during administration of low oxygen gas mixtures. When the oxygen saturation of hemoglobin fell but yet exceeded 55 per cent there was usually a rise in resistance in the pulmonary bed without change in flow. Below a saturation of 55 per cent the cardiac output rose and the P_{PA} fell, indicating that in the face of so severe a strain the circulatory restrictions were swept away in adaptations which served the urgent need for a maximal total flow.

These various observations in the experimental animal have established the fact that the vascular bed of the lungs reacts to changes in gas tensions in the alveolar environment. Before discussing the over-all picture it is planned first to survey the related information which has been derived from studies on man. Shortly after von Euler & Liljestrand's description of the effects of hypoxia in the cat, Motley et al. (141) reported the first of such experiments in normal man. Exposures to 10 per cent O_2 for 10 min. periods resulted in a mean rise of P_{PA} of 10 mm. Hg. while cardiac output fell a little less than 10 per cent. In a subsequent more elaborate study from the same laboratory Fishman et al. (83) examined the effects of hypoxia in a large group of patients with heterogeneous chronic pulmonary diseases. In order to establish a steady state to insure greater accuracy in determining cardiac output by the direct Fick method, these patients were subjected to various low oxygen gas mixtures varying from 10 up to 18.5 per cent. After the steady state was attained there was little change in cardiac output and in only one-third of the 35 patients did P_{PA} rise more than 5 mm. Hg. Westcott et al. (183) recorded the influence of 13 per cent O_2 inhalation on P_{PA}, P_{PC}, and cardiac output in 21 subjects free from cardiopulmonary disease and in 11 patients with various forms of cardiac, pulmonary, and mixed disease. In almost every instance there was a rise in P_{PA} and the concurrent changes in P_{PC} were insignificant or showed no consistent trend. The mean change in cardiac output was insignificant although there were instances of rise, of fall, and of phasic changes. As calculated from these data the pulmonary vascular resistance appeared to have risen in each case, and the authors conclude from internal evidence that the rise in resistance was not correlated with changing cardiac output. These conclusions have been held to be invalid by Fishman et al. because the measurements were made during an unsteady state obtaining during the first 10 or more minutes of acute exposure to hypoxia. There is no gainsaying the advantages and, sometimes, the cardinal

necessity for attaining steady state for many functional measurements; however, "steady state" is a relative term, for while certain ventilatory functions exhibit a plateau other functions may begin to change during the period required to reach a steady state. Inspection of the data presented by Westcott *et al.* suggest that while the absolute figures may be subject to errors inherent in unsteady state measurements, nevertheless, the direction and values of the changes probably do indeed characterize the over-all reaction. In further experiments they could find no vascular response to the inhalation of 5 per cent CO_2. Doyle, Wilson, and Warren (65) made observations on the effect of 10 per cent oxygen which answered certain of the questions raised subsequently by Fishman *et al.* In both normal subjects and in patients with various cardiopulmonary abnormalities they measured cardiac output both by gas exchange and by dye-dilution methods. The latter technic yields a virtually instantaneous measurement not affected by transients in gas exchange. In the normal group as the ΔP across the lung widened, the cardiac output tended to increase but the pulmonary vascular resistance rose in every instance, and the mean increase was 80 per cent. In the abnormal group no such consistent response was observed: in some the pattern mimicked that of the normal subject, in others changes in P_{PC} and cardiac output were so related as to indicate that resistance was raised in some, lowered in others, and underwent no change in still others. No real correlation between clinical state and direction of pulmonary vascular response could be made out.

The evidence is less clear-cut that enrichment of the oxygen content of alveolar air reduces the resistance through the lung. Fishman *et al.* (83) found equivocal changes. In a small group of normal subjects Westcott *et al.* (183) found no effect of 100 per cent oxygen, whereas, in five subjects with pulmonary arterial hypertension, 100 per cent O_2 inhalation led to significant falls in P_{PA}, which resumed its earlier levels when the patients breathed room air again. Dressler *et al.* (67) record the small and possibly significant fall in P_{PA} which follows the administration of 100 per cent oxygen to patients with pulmonary tuberculosis or mitral stenosis. Critical evidence to establish the basis for the fall was not available.

The evidence derived from these experiments in man furnishes ample support for the view that these are adjustments in alveolar perfusion tuned to changes in gas mixtures ventilation and that they agree in general principle with similar experiments in animals. The rather vague quality of the preceding sentence is deliberate because, clearly, there is no one single reactive pattern to one single stimulus. Consider the following pairs of observations, selected from the material which has been reviewed: lowering of inspired P_{O_2} raises vascular resistance in normal subjects, but may have no such effect in some patients with pulmonary disease, and if lowered to extremes in the dog may induce vasodilatation; the role of the central nervous system in this response to hypoxia is demonstrated by the effect of sympathectomy, and yet there is ample evidence that a local response may be evoked when all central connections have been severed. Superficially these facts may appear

to be mutually contradictory, but this is so only in the case of an attempt to oversimplify what is an extraordinarily complex system susceptible to many opposing influences. The usefulness to the organism of a mechanism for adjusting perfusion to alveolar gas composition is plain, but if carried to a ridiculous extreme this response might be responsible for shutting off entirely the flow through the lung. Apparently under certain circumstances, and perhaps more segmental than general in distribution, perfusion of areas impoverished with respect to their supply of oxygen is reduced. This reduction in perfusion may be minimized or indeed reversed under extreme stress or in the case of extensive pathological change. It is unlikely, therefore, that a simple causal relation exists between the pulmonary vascular resistance or one of its factors, P_{PA}, and some other ventilatory derivative such as the degree of saturation of oxyhemoglobin in systemic arterial blood. In fact, however, the statistical correlation of these two factors is of a high order as shown by Harvey (109), Mounsey (142), Fowler (86), and Yu (189) and their colleagues so that it seems justified to conclude that within certain limits arterial oxygen saturation is a rough linear gage of the factors tending to increase resistance to flow through the lung. Similarly, Harvey *et al.* (109) and Yu *et al.* (189) have shown a high degree of correlation between P_{PA} and the CO_2 tension of arterial blood in patients with pulmonary emphysema. As underlying pulmonary disease becomes more severe the supervention of myocardial failure may introduce additional factors which then make such simple correlations difficult to extract from the final complex situation (55, 56, 81, 110).

Despite these difficulties there appear to be certain relationships which are of importance in understanding pathogenesis and treatment of diffuse pulmonary disease. And to summarize, we may return to the outline presented earlier of the factors which affect the flow of blood through the lungs. Refinements in technic and more extensive search have revealed lately that the geometrical factors in the structure of the pulmonary circuit are susceptible to impressive alteration under the stress of disease. In addition to the better known changes having to do with progressive obliteration of the pulmonary arterial supply, there are the factors introduced by the luxuriant expansion of the bronchial circulation and by the probability that virtual arterio-venous shunts may operate. There is as yet no knowledge of the pressure relations existing at the junctions of pulmonary and bronchial circulations but what evidence is available indicates clearly that large fractions of the venous return to the left atrium may not have arisen from the right ventricle. The methods for estimating the volume of blood in the lungs as distinguished from that in the heart still lack high enough resolution to permit confident prediction of the actual changes which occur, but awareness is growing that this volume must be taken into account. Elegant technics are providing more and more information concerning certain pressures and pressure gradients within the vasculature of the lung; and extensive changes which accompany pulmonary disease have been described. Virtually nothing is known regarding the roles played by the laminarity of flow and viscosity

of blood. Except in unusual circumstances there is no suggestion that these factors are sufficiently variable to introduce much disturbance in pulmonary flow. Despite the undoubted potent effects on pulmonary flow and pressure of the capacity and behavior of the cardiac pump, evidence has accumulated steadily to indicate that reactivity of the pulmonary bed and the vasomotion, or its equivalent, which the bed displays are factors which must be taken into account. There has been shown to exist both receptor and effector mechanisms for changing resistance to flow; their activity at rest and in health probably is slight, but during work and in disease their effects may become crucial. The influences which play on these mechanisms are diverse and extensive; and their algebraic sum may be difficult to predict or to factor. Their resultant perhaps may be characterized one day by some study of the critical closing pressures, a fresh concept introduced by Burton and his colleagues, but not yet measured in the pulmonary circulation. Many of the alterations which occur may be interpreted in the light of the apparent adjustments which maintain an optimal ratio between alveolar ventilation and perfusion, but it is equally clear that under extreme environmental or pathological stresses the teleological prediction may be misleading. The crux of this relation essentially is the area of the vascular bed available for transfer of respiratory gases between the contents of the alveoli and the blood traversing them. This special aspect is to be reviewed below.

DIFFUSION OF GASES

In the early years of this century, interest in the transfer of gases between the alveoli and the blood centered on the question of active secretion of oxygen by the cells of the lung. With the demonstration that oxygen secretion was unnecessary to account for gas exchange and was highly improbable even as an accessory mechanism, interest was focussed again on the diffusion characteristics of the lungs. A method for the determination of diffusing capacity had been evolved under the stimulus of the controversy over oxygen secretion, and the order of magnitude of the diffusing capacity, both at rest and during exercise, was known. There remained, therefore, three main avenues for further study: (a) a more detailed description of the size of the diffusing capacity in various physiological and pathological states; (b) an analysis of mechanisms controlling the size of the diffusing capacity in any given state; and (c) basic research into the characteristics of the reaction of CO and O_2 with hemoglobin and of diffusion within the blood itself. The latter subject is beyond the scope of this review. Both of the first two types of study were dependent upon improved methods for studying the diffusing capacity. Within the past decade improvements in methodology have occurred, and much of the present review deals with these technical matters and with the advances in the descriptive phase of the subject which have followed the introduction of new technics. At present, interest appears to be shifting to the analysis of mechanisms controlling the diffusing capacity in health and disease.

In the simplest terms, the diffusing capacity is a function of the total area of the diffusing surface and of the permeability of this surface per unit area. Concerning moment to moment changes in permeability our knowledge is very meager and goes little beyond Krogh's early estimate of the amount of thinning of the membrane which, on geometric grounds, might accompany expansion of the lungs. Changes in permeability resulting from physicochemical changes, while theoretically possible and important (150), remain entirely unexplored. On the other hand, there is good reason for the belief that the total area of the diffusing surface, which is the same, for practical purposes, as the area of the walls of the active capillaries, may change appreciably from moment to moment. Wearn et al. (179) have observed such changes directly in the unopened chest of the cat, and from what is known of capillary function in other organs it seems highly probable that moment to moment changes occur in the human lungs. Confronted with ignorance regarding permeability changes and promising possibilities in the case of variable capillary activity, we find ourselves at present looking for additional clues to the relationship between diffusing capacity and the size of the active capillary bed of the lungs. If it should turn out that diffusing capacity is controlled by the same mechanisms which control the size of the active capillary bed, then this survey will have become an appropriate sequel to the preceding section on the pulmonary circulation.

DIFFUSING CAPACITY: CONCEPTS AND METHODS

The diffusing capacity of the lungs is the amount of gas which diffuses into the blood per minute per mm. Hg of pressure gradient across the alveolar membrane. This membrane includes the entire tissue-fluid barrier between the alveolar gas and the hemoglobin molecule; i.e., the alveolar wall, the capillary endothelium, the blood plasma, and the membrane and contents of the red cell. The analysis of diffusion requires an estimation of partial pressure gradients of gas between the alveolar and the capillary blood phases. Inert gases, such as nitrogen, nitrous oxide, helium, etc., which only dissolve in the blood and have no special affinity for hemoglobin, saturate the blood early in its course through the alveolar capillary, and no measurable gradient remains at the end of the capillary. Because, in calculating the mean diffusion gradient, it is essential to know the gradient at the end of the capillary, these inert gases are unsuitable for use in determining diffusing capacity. In practice, only carbon monoxide and oxygen, which have great affinity for hemoglobin, have proved satisfactory, and in each case carefully chosen conditions have to be satisfied in order to make possible a quantitative estimation of the mean alveolo-capillary diffusion gradient. Determination of this gradient has always been the difficult methodological problem in estimating diffusing capacity. In general, when a gas diffuses from the alveoli into the capillary blood or vice versa, the diffusion gradient diminishes from point to point along the course of the capillary as the partial pressures in the gas phase and the blood phase approach equilibrium. The mean gradient is

that hypothetical diffusion gradient which, if present continuously along the entire course of the capillary, would permit exactly the same amount of gas to diffuse as actually does diffuse. The mean gradient thus represents in a single figure the net physiological effect of an ever-changing gradient. When the total amount of gas diffusing per minute is divided by the mean gradient, the amount diffusing per mm. Hg is derived; *i.e.*, the diffusing capacity of the lung, D_{O_2}.

Bohr (20), writing in 1909, made the original contributions in the field of pulmonary diffusion on which all subsequent determinations of diffusing capacity have been based. The particular contributions to which we refer can be summarized by saying that he pointed out two different ways of obtaining the mean diffusion gradient, one for CO and one for O_2. He recognized that, under properly chosen conditions, measurable quantities of CO would diffuse into the pulmonary capillary blood without producing a significant partial pressure of CO in the blood, owing to the remarkable affinity of hemoglobin for CO. This was a major advance since it provided a means of bypassing the knotty problem of determining the mean P_{CO} existing in the alveolar capillaries. When this mean capillary P_{CO} is taken to be zero, the mean alveolo-capillary gradient becomes simply the alveolar P_{CO}. The Kroghs (123, 124) immediately made use of this concept in their methods for determining diffusing capacity, and recently Filley (82) has developed an important modification which resembles even more closely the original Bohr approach. The assumption that mean capillary P_{CO} is zero is, like so many useful premises, not strictly true, and Roughton (165, 166) and Forbes, Sargent, and Roughton (84) have provided increased knowledge of the factors which affect this pressure. The Bohr assumption of zero back pressure, nevertheless, made possible determinations of diffusing capacity of sufficient accuracy to add greatly to the understanding of pulmonary gas exchange and to help disprove Bohr's own belief in oxygen secretion. The diffusing capacity method of Lilienthal *et al.* (133) in which oxygen is used as the test gas, was made possible by Bohr's method for calculating the mean partial pressure gradient of oxygen. Bohr's ideas thus form an integral part of the three methods for determining diffusing capacity which currently are in use.

Bohr's work came at a time when a spirited controversy raged over the question of active secretion of oxygen by the cells of the lung. Was the transfer of oxygen by the lungs to the blood accomplished solely by diffusion or did active secretion of oxygen also occur under certain conditions of stress? Bohr's reasoning on this subject (20) is of historical as well as physiological interest and can be described in relation to the formula for diffusing capacity:

$$D_{O_2} = \frac{\dot{V}_{O_2}}{P_{A_{O_2}} - \overline{P}_{c_{O_2}}}$$

where D_{O_2} = diffusing capacity, V_{O_2} = amount of oxygen in ml. diffusing per minute, and $P_{A_{O_2}} - \overline{P}_{c_{O_2}}$ = the mean pressure gradient of oxygen in mm. Hg between the alveolar gas and the blood in the alveolar capillaries. Having

devised a method of integration whereby the mean gradient could be calculated when the partial pressure gradients at both ends of the alveolar capillaries were known, Bohr proceeded to calculate the mean gradient, $P_{A_{O_2}} - \bar{P}_{c_{O_2}}$, for various hypothetical conditions, assuming that gas exchange took place solely by diffusion. He then estimated the diffusing capacity, D_{O_2}, using data which Haldane had obtained in the course of experiments with carbon monoxide on resting human subjects. An actual value for oxygen consumption, $\dot{V}_{O_2}$, was taken from the work of Zuntz, Loewy, Müller, and Caspari, who had studied a subject during exercise at high altitude on Monte Rosa, where the barometric pressure was 450 mm. Hg. Bohr found that the product of diffusing capacity (estimated for the resting state) times the mean gradient (estimated for exercise at altitude) was much less than the measured oxygen consumption during exercise at altitude. He reasoned that the diffusing capacity was too low to account for oxygen uptake by the lungs under the stress of exercise at high altitude and adopted the belief that active secretion of oxygen had occurred to make up the difference. Bohr was approximately correct, according to modern calculations, in his estimates of mean gradient, but he failed to realize the extent of variations in diffusing capacity existing between different persons, and between rest and exercise in a given subject. His calculations, therefore, led to an erroneous conclusions.

The controversy over oxygen secretion is said to have started when Ludwig suggested that something other than simple diffusion might be necessary to account for gas exchange. Pflüger (1871), however, obtained results which were consistent with the diffusion theory. Then Bohr (1890), using the aerotonometer, found evidence in favor of active secretion. Fredericq (1894) favored simple diffusion, but Bohr (1909) then advanced the impressive evidence, reviewed above, in favor of secretion. In 1910 August and Marie Krogh (121, 122, 123) presented the first of their comprehensive and convincing papers in favor of diffusion. This was followed in 1912 by Douglas & Haldane (61) who ranged themselves on the side of oxygen secretion and presented the last important evidence in defense of this point of view. Their approach to the problem of determining the P_{O_2} of blood leaving the alveolar capillaries was extremely ingenious, but inadequate technical methods led them to believe that this value frequently exceeded the alveolar P_{O_2}. That same year Hartridge (108), using the same approach but improved analytical technics, found that alveolar P_{O_2} was invariably higher than the P_{O_2} of the blood. While recognizing his findings as evidence against the theory of oxygen secretion, Hartridge failed to press the point. In 1915, Marie Krogh (124), using improved technics for the determination of diffusing capacity, settled the matter in favor of the diffusion theory. Her determinations during exercise indicated that oxygen consumption could always be accounted for by the product of diffusing capacity times mean gradient. The Kroghs possessed the technical skill and insight which, when added to Bohr's extraordinary scientific imagination, led to the solution of this complicated problem.

The Krogh method.—Marie Krogh (124) described what has come to be considered the classical method for determining diffusing capacity, using CO as the test gas. This is a single breath method in which the subject takes a deep breath of a gas mixture containing CO, usually less than 0.5 per cent and immediately exhales approximately one-half of his vital capacity and then holds his breath. The last portion of this partial expiration is analyzed for CO and is considered representative of the alveolar gas at the start of the period of breath holding. The breath is held for about six seconds and the subject then gives a second sharp and deep expiration. The alveolar sample from the end of this expiration is analyzed to give the concentration of alveolar CO at the end of the breath-holding period. From the difference in the CO concentrations at the beginning and end of the period, the amount of CO diffusing into the blood can be calculated, provided the volume of gas in the alveoli during this period is known. The latter information is derived from separate determinations of residual volume and of respiratory dead space, and from a spirometric tracing which shows the volume changes during the experiment. The mean partial pressure gradient of CO between alveolar gas and capillary blood is considered equal to the mean alveolar partial pressure as suggested by Bohr. The mean alveolar P_{CO} is not an arithmetic average of the concentrations at the beginning and end of the experiment, however, since the rate of change in concentration is assumed to be a function of the concentration which is present at any given instant. The mean alveolar P_{CO} must be calculated, therefore, by means of the integral calculus. The CO uptake for the entire lung, when divided by the mean alveolar P_{CO}, gives the diffusing capacity of the lung for CO. Because of the difference in the diffusion characteristics of O_2 and CO, the diffusing capacity for O_2 is considered to be 1.23 times the diffusing capacity for CO.

The assumption of zero P_{CO} in the blood has been shown by Roughton (166) to introduce a significant error when the partial pressure of O_2 in the blood is high, and an indeterminate but smaller error may result when the CO is mixed with air. Furthermore, the method of sampling alveolar gas may not give a representative value for alveolar gas concentration, particularly in subjects with pulmonary disease. And finally, recent experiments indicate that the rate of change of alveolar P_{CO} is not the simple exponential one assumed by Krogh and that the calculated value for mean alveolar P_{CO} may therefore be in error. In spite of these reservations, Krogh's values have been accepted as approximately correct and are in the same range as the values found by the other two methods currently in use.

The method of Lilienthal, Riley, Proemmel, and Franke.—The method of Lilienthal *et al.* (133) is a steady state method in which oxygen itself is used as the test gas. In this case the amount of oxygen diffusing is the same as the oxygen consumption of the subject under the conditions of the experiment. The mean alveolo-capillary diffusion gradient is estimated, using a modification of Bohr's graphic integration procedure (159), from a knowledge of the gradient at each end of the capillary and the shape of the oxyhemoglobin

dissociation curve. Standard dissociation curves may be used for virtually any subject, but the P_{O_2} in alveoli, in mixed venous blood, and in blood leaving the alveolar capillary (end-capillary P_{O_2}) must be determined for the particular conditions of the experiment. This involves the simultaneous sampling and subsequent analysis of arterial blood, mixed venous blood, and expired gas, with the subject breathing room air and then breathing a low oxygen gas mixture. The alveolar P_{O_2} is derived indirectly from the inspired P_{O_2}, the arterial P_{CO_2}, and the $CO_2 - O_2$ exchange ratio (162). The P_{O_2} of the mixed venous blood can be determined from a direct sample from the pulmonary artery, or an estimate can be used which is based on knowledge of the approximate size of the arterio-venous oxygen difference. The end-capillary P_{O_2} is calculated from the alveolar-arterial P_{O_2} gradients at the two different levels of oxygenation. From estimates of the diffusion gradients at both ends of the alveolar capillaries, one can calculate the mean gradient. The oxygen consumption, when divided by this gradient, gives the diffusing capacity.

This method is complicated by the necessity for determining or otherwise estimating the P_{O_2} of the mixed venous blood. Although, for purposes of obtaining an accurate determination of diffusing capacity, it is not necessary to know the gradient at the proximal end of the capillary with as much precision as the gradient at the distal end, the use of assumed values for mixed venous blood may lead to significant errors. Catheterization of the pulmonery artery is an obvious solution but limits the applicability of the method in normal subjects and during strenuous exercise. Difficulties also arise owing to the necessity for reaching an approximately steady state during low oxygen breathing, however, present experience suggests that no significant errors are introduced if samples are taken after 15 min. in the case of resting subjects (29) and after a somewhat shorter time during treadmill exercise (164). All calculations involving blood gas tensions suffer from the limited accuracy of available technics for determining them. The indirectly determined values for alveolar P_{O_2} are a distinct advance over those obtained from direct samples, especially in the presence of pulmonary disease. Also in favor of this method is the fact that the subject does not have to perform any special ventilatory maneuvers. The theoretical and technical aspects of the direct oxygen method have been explored further by Riley & Cournand (159), Riley, Cournand & Donald (160), Riley, Riley & Hill (163), Carroll, Cohn & Riley (29), and Riley *et al.* (164).

The method of Filley.—Recently Filley (82) has devised a steady state method for determining diffusing capacity by means of CO. He calculates alveolar P_{CO} by an indirect method which corresponds to the indirect method used by Lilienthal *et al.* for determining alveolar P_{O_2}. Arterial P_{CO_2} is taken to be equivalent to alveolar P_{CO_2}, and alveolar P_{CO} is calculated from this value and from determination of the concentrations of CO_2 and CO in inspired and expired air. A low concentration of CO is breathed for a time short enough that very little back pressure of CO builds up in the pulmonary capillary blood. The alveolar P_{CO} is taken accordingly as the mean alveolo-

capillary tension gradient of CO. Uptake of CO, as determined from the inspired and expired gases, is divided by the alveolar P_{CO} to give a value related to the diffusing capacity for CO. Filley is reluctant to call this the diffusing capacity because of uncertainty regarding the assumption that pulmonary capillary P_{CO} is zero.

This method takes advantage of some of the best aspects of both the Krogh method and the direct oxygen method of Lilienthal *et al.*, but is also subject to some of the same limitations. It seems unlikely that the indirect calculation of alveolar P_{CO} can be used successfully in patients with poor intrapulmonary mixing of gases because of the limited period of time which is available for the distribution of CO throughout the lungs. At the present writing it is too early to give an adequate evaluation of the Filley method.

DIFFUSING CAPACITY: APPLICATIONS

Findings in normal subjects.—Krogh found values for diffusing capacity in normal subjects which varied between 23 and 43 at rest and between 37 and 56 during exercise (124). Lilienthal *et al.* (133) obtained values between 12 and 36 at rest and between 50 and 76 during exercise. Filley's results (82), as yet unpublished, are in the same range. The extent of this agreement between independent workers using three different methods is remarkably good and leaves little doubt concerning the order of magnitude of the diffusing capacity of the lungs in normal subjects.

An effort to describe in more detail the changes which occur in diffusing capacity with increasing grades of work has been made with all three methods. Bøje (21), using Krogh's method, noted a tendency for the diffusing capacity to increase at first and then to level off as the work load was further increased. These findings were not clear cut or striking. Riley and co-workers (164), using the method of Lilienthal *et al.*, found a sharp increase in diffusing capacity as oxygen consumption increased up to about 1200 ml. per min. At higher work loads and higher values for oxygen consumption there was no further increase in diffusing capacity. This value was called the maximal diffusing capacity. Filley (82), using his CO method, found similar evidence that a maximal value for diffusing capacity could be reached and measured. Both Riley *et al.* and Filley found a rather sharp inflection of the curve of diffusing capacity against oxygen consumption at the point where the steeply rising curve flattened out at the maximal value. The possible significance of this inflection in relation to hemodynamic changes affecting the capillary bed will be discussed in more speculative fashion below.

The finding of maximal values for diffusing capacity suggested the interpretation that the capillary bed, which provides the diffusing surface, was fully expanded when the diffusing capacity was maximal. It was presumed that further increase in diffusing capacity was limited by the structural characteristics of the diffusing surface and that, therefore, these structural characteristics could be defined quantitatively by the maximal diffusing capacity. Without defining precise mechanisms, it was thought likely that

parts of the capillary bed closed down at milder grades of work or at rest,
thus reducing the area of the diffusing surface and hence the diffusing capac-
ity. Significant changes in the thickness of the alveolar membrane or in the
diffusion characteristics per unit area were thought to be a less likely explan-
ation of the findings. The interpretation was well summarized by the concise
statement of Barcroft (13) who wrote that "the two most obvious means of
securing [an increase in diffusing capacity with exercise] are distension of
the lung, which makes the cells thinner, and the opening up of vascular
areas, either by increasing the calibre of vessels already open, or opening up
those hitherto shut."

To test these suggestions further, it seemed essential to determine the
maximal diffusing capacity in normal subjects of different ages. Twenty-
one males between the ages of 17 and 76 were studied by Cohn et al. (33).
The subjects walked on a motor-driven treadmill and exercised at levels close
to maximal capacity under the conditions of the experiments. The data
showed considerable scatter, but there was a definite downward trend,
indicating a rather marked decrease in diffusing capacity with age. This was
interpreted as suggesting a reduction in total pulmonary capillary area with
increasing years. The data thus provided not only normal standards with
which to compare the maximal diffusing capacities of patients with pul-
monary disease, but also another semiquantitative gage of the degenerative
changes in a vascular bed which accompany the aging process.

Findings in pulmonary disease.—The application of the diffusing capacity
determination to the analysis of disease states was begun by Krogh in 1915
(124). She showed that the diffusing capacity during rest tended to be low
in a variety of pulmonary disease. This work was somewhat unsatisfactory
because of uncertainties regarding the validity of direct alveolar samples in
patients whose alveolar P_{CO} well may have varied significantly in different
parts of the lungs. Donald et al. (60) recently published extensive data, in-
cluding diffusing capacity determinations by the oxygen method, on 32 pa-
tients. These patients suffered from fibrosis and emphysema, and were ana-
lyzed according to the classification of Baldwin, Cournand & Richards (11,
12). In all categories the resting diffusing capacity was found to be below
15, which was taken as the lower limit of the normal range. The reduction
in diffusing capacity was least pronounced in patients with pulmonary fibro-
sis, Group 1, which resulted from tuberculosis and silicosis. The patients
with fibrosis, Group 2, involving the diffusing surface itself, showed very
severe impairment, and the patients with emphysema showed diminishing
diffusing capacity proportional to the severity of the emphysema. The
emphysematous patients in Group 4 had associated cor pulmonale, and their
diffusing capacities were extremely low. The lowest value recorded was 4
ml. of oxygen per min. per mm. Hg of oxygen pressure gradient, and this
value occurred in three patients. The low values were interpreted to have
been the result of either (a) decrease in the permeability of the pulmonary
membrane per unit area or (b) decrease in the total area of the membrane.
The low values found in the second group of patients with fibrosis was

thought to be accounted for in large part by the first mechanism, and the low values in emphysema were attributed to the second. Obviously both mechanisms can, and probably often do, operate simultaneously in the same patient. Any interpretation regarding mechanisms, however, must be based on associated clinical and pathological evidence and not on the physiological studies alone.

An intensive study of the patients with pulmonary fibrosis, Group 2, was published by Austrian et al. (6). In this paper the vivid term "alveolar-capillary block" was introduced, to identify "a syndrome caused by a variety of pathologic processes and characterized histologically by alterations of the pulmonary diffusing surface, i.e., the alveolar-capillary septa, and physiologically by a reduction in the diffusing capacity of the lungs." To quote further from Austrian et al.,

The group of subacute or chronic diseases which leads to this syndrome have common clinical characteristics, prominent among which are the diffuse, finely dispersed pulmonary lesions as revealed by x-ray and those signs and symptoms which result from the physiologic disturbances. . . . The pattern of pulmonary dysfunction consisted of (1) reduced lung volumes, (2) maintenance of a large maximum breathing capacity, (3) hyperventilation at rest and during exercise, (4) normal or nearly normal arterial oxygen saturation at rest but a marked reduction of the arterial oxygen saturation after exercise (standard one minute step test), (5) normal alveolar oxygen tension, (6) a reduced oxygen diffusing capacity and (7) pulmonary arterial hypertension.

Whether because of increasing incidence of cases or improved recognition, the syndrome of alveolar-capillary block has aroused heightened interest during recent years. One of its interesting and edifying characteristics is the fact that it now can be identified usually on clinical grounds alone, in spite of the fact that the elucidation of the altered physiology required extremely elaborate physiological tests. Among patients in general the most common cause of functional disability attributable to pulmonary disease is ventilatory insufficiency resulting from airway obstruction. By contrast, patients with the alveolar-capillary block syndrome have no airway obstruction or signicant ventilatory impairment, and free breath sounds can be heard over all parts of the lungs. These findings together with manifest hyperventilation provide convincing clinical evidence that a normally adequate or higher alveolar P_{O_2} exists. When cyanosis on exertion is also present, localization of the block in oxygen transport at the alveolar-capillary level is suggested strongly, assuming that no vascular shunting is present. If the roentgenogram of the chest is consistent, there may be no need to apply more elaborate tests to establish the functional diagnosis of impaired diffusion. The etiological diagnosis, on the other hand, may be difficult if not impossible to establish. Among the cases reported by Austrian et al. there were three who had been exposed to beryllium, two who had Boeck's sarcoid with diffuse pulmonary involvement, one who had scleroderma of the lungs, and six who had pulmonary fibrosis or granulomatosis of unknown cause.

Carroll et al. (29) determined the resting diffusing capacity in patients

with mitral stenosis. In some, values were normal while in others there were varying degrees of impairment. Evidence was presented which suggested that marked impairment of diffusing capacity was not accounted for adequately by the amount of pulmonary edema which these patients may have had. It was pointed out that both structural and functional factors affecting the pulmonary capillary bed might well be operating since abnormalities of both types are known to occur in mitral stenosis. Because the hemodynamic alterations might have a significant effect upon the size of the pulmonary capillary bed in resting patients, the values for diffusing capacity at rest were not considered to provide an adequate evaluation of the diffusion characteristics of the entire capillary bed in this disease. It was thought that maximal diffusing capacity determinations would be essential to provide this information.

Riley, Riley & Hill (163) studied intensively three patients with diffuse pulmonary sarcoidosis. Diffusing capacity determinations were repeated as many as 12 times during the course of therapy with corticotropin in one patient. This study represented the first extensive use of the maximal diffusing capacity in following the course of a disease process. All three of these patients fell in the group defined by Austrian *et al.* as having alveolar-capillary block, and all three had very low diffusing capacities at rest, varying between 3 and 8 per sq. m. of body surface. The value, 10 per sq. m., was considered to be the lower limit of the normal range. The maximal diffusing capacities varied between 8 and 16 per sq. m., as compared to predicted normal values varying between 23 and 40 per sq. m. The predicted normal values were admittedly no more than rough approximations because only a few normal subjects had been studied at that time, but they sufficed to indicate that the patients' maximal diffusing capacities were much impaired. The vital capacities, maximal breathing capacities, and arterial oxygen tensions of these patients showed marked increases in response to corticotropin and there was striking diminution in the diffuse nodulation as demonstrated by x-ray. The maximal diffusing capacity, on the other hand, changed very little in response to therapy. According to the authors,

A reasonable explanation for this apparent paradox can be deduced from the pathological changes. When a sarcoid nodule develops it probably destroys the alveolar capillaries which previously occupied the same space. The total diffusing surface of the lungs is thereby reduced and gas exchange is largely diverted to the remaining relatively normal segments of alveolar wall lying between sarcoid nodules. Resolution of the nodule is probably not accompanied by restoration of the destroyed capillaries, so there is little increase in diffusing surface or in diffusing capacity after ACTH therapy.

Other studies have tended to confirm this impression that damage done to the pulmonary capillary bed is irreversible (137).

The current status of diffusing capacity measurements can be summarized as follows. The three available methods are in essential agreement regarding the size of the diffusing capacity in normal persons at rest and during exercise.

The recently introduced concept of maximal diffusing capacity is useful in evaluating the total diffusing surface of the lungs. Application of this technic to normal males of different ages has provided normal standards and has demonstrated an impressive diminution in diffusing capacity with increasing years. While the exact mechanism of this diminution is not known, it is thought likely to be the result of a progressive reduction in the number of pulmonary capillaries. In disease states the low oxygen method of Lilienthal *et al.* has been used most extensively. Low values have been found in the group of diseases characterized by alveolar-capillary block, where the alveolar membrane is thickened or infiltrated, and in emphysema, where the alveolar membrane is reduced in area. On theoretical grounds it would seem that reduction in diffusing capacity would invariably have to be explained in terms of these prototypes; *i.e.*, reduction in total area of diffusing surface or reduction in permeability per unit area or both. Differentiation between these mechanisms and further decision as to the structural or functional nature of changes in the capillary bed must be made on the basis of additional clinical, pathological, or physiological evidence.

It would not be fitting to close this section without mentioning that fascinating challenge to the physiologist, namely, the use of the diffusing capacity of the lungs as a tool with which to explore other aspects of pulmonary function. Roughton (166) provided a superb example of ingenuity in his calculations of the volume of blood in the pulmonary capillaries and the average time spent by the blood in the pulmonary capillaries. By combining both chemical and physiological data related to the reaction between CO and oxyhemoglobin, Roughton was able to calculate that the volume of blood in the capillaries was roughly 60 ml. at rest and 95 ml. during hard work. The time spent in the capillaries by a unit volume of blood was estimated to be $0.75 \pm .25$ second at rest and $0.34 \pm .10$ second in hard work. In view of Roughton's careful analysis of possible errors in the calculations, there is little doubt that these values represent the correct order of magnitude.

Hatch (111) has developed an interesting mathematical analysis by which he undertakes to identify the relative importance of ventilation, circulation, and diffusion in determining the uptake of CO under various conditions. He treated CO as if it were an inert gas with high physiological "solubility" and extended Henderson and Haggard's type of analysis of exponential transfer coefficients. By choosing appropriate exponents he was able to develop a mathematical expression which fit the data of Forbes, Sargent & Roughton (84). In view of the simplifying assumptions which were made, the importance of this ingenious and potentially valuable contribution must await further demonstration that the physiological deductions are reliable.

Barcroft (13) was among the first to associate the increase in diffusing capacity with exercise with possible activity of the pulmonary vasomotor system. More recently, Burton and his colleagues (26, 27, 143) have described certain characteristics of small vessels which increases the probability of this

association. They brought together theoretical and experimental evidence to show that small vessels in certain circuits shut completely at a critical closing pressure greater than zero. This pressure was shown to be increased greatly by the presence of vasomotor tone. In order to relate these vascular phenomena to the diffusing capacity, we add the suggestion that complete closure of some small pulmonary vessels would presumably cut off flow through adjacent portions of the capillary bed and would thereby reduce the diffusing capacity. Hence, if vasomotor tone and complete closure of small vessels below a critical pressure both occur in the lungs, they should be factors of great importance in determining the size of the diffusing capacity under any given conditions. If all this be true, and it is still conjectural, then, conversely, evaluation of changes in the diffusing capacity might well help to define the patterns of flow through the alveolar bed.

As was noted earlier, the rapid rise in diffusing capacity at increasing grades of work, and the abrupt leveling off of the diffusing capacity at a maximal value is not the expected behavior of a simple elastic system. It suggests rather that previously closed capillaries may open abruptly when a critical closing pressure is exceeded. Such a concept is strengthened by the parallel finding of Cournand et al. (36) and Dexter et al. (54) that pulmonary arterial pressure fails to increase with increasing grades of work until a critical rate of blood flow through the lungs is reached. From these sets of data it is apparent that the grade of work which produces the maximal diffusing capacity is approximately the same as that which produces the first increase in pulmonary arterial pressure. This would be consistent with the concept of a vascular bed which is wide open when a critical pressure has been exceeded, and one which operates at low pressures with very small external restraining pressures.

Even when allowance is made for the speculative nature of the remarks in these final paragraphs, it becomes increasingly clear that there is a close relationship between the pulmonary circulation and the pulmonary diffusing capacity. Indeed, as was implied at the outset of this review, they are warp and woof of the same functional fabric.

LITERATURE CITED

1. Ameuille, P., and Lemoine, J. M., *Bull. soc. méd. hôp. Paris* 50, 1649–57 (1934)
2. Ankeney, J. L., *Am. J. Physiol.*, 169, 40–49 (1952)
3. Ankeney, J. L., *Circulation Research*, 1, 58–61 (1953)
4. Araujo, J., and Lukas, D. S., *J. Clin. Invest.*, 31, 1082–88 (1952)
5. Atwell, R. J., Hickam, J. B., Pryor, W. W., and Page, E. B., *Am. J. Physiol.*, 166, 37–144 (1951)
6. Austrian, R., McClement, J. H., Renzetti, A. D., Jr., Donald, K., Riley, R. L., and Cournand, A., *Am. J. Med.*, 11, 667–85 (1951)
7. Aviado, D. M., Jr., Cerletti, A., Alanis, J., Bulle, P. H., and Schmidt, C. F., *Am. J. Physiol.*, 169, 460–70 (1952)
8. Aviado, D. M., Jr., Li, T. H., Kalow, W., Schmidt, C. F., Turnbull, G. L.,

Peskin, G. W., Hess, M. E., and Weiss, A. J., *Am. J. Physiol.*, **165**, 261–77 (1951)

9. Aviado, D. M., Jr., and Schmidt, C. F., *Circulation*, **6**, 666–80 (1952)
10. Bahnson, H. T., *J. Appl. Physiol.*, **5**, 272–76 (1952)
11. Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr., *Medicine*, **28**, 1–26 (1949)
12. Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr., *Medicine*, **28**, 201–37 (1949)
13. Barcroft, J., *Features in the Architecture of Physiological Function* (University Press, Cambridge, England, 368 pp., 1938)
14. Bayliss, R. I. S., *Brit. Med. Bull.*, **8**, 354–57 (1952)
15. Bean, J. W., Mayo, W. P., O'Donnell, F., and Gray, G. W., *Am. J. Physiol.*, **166**, 723–32 (1951)
16. Berggren, S. M., *Acta Physiol. Scand.*, **4**, Suppl. 11 (1942)
17. Berry, J. L., and Daly, I. de B., *Proc. Roy. Soc. (London)*, [B.] **109**, 319–36 (1932)
18. Binet, L., and Bourliere, F., *Compt. rend. soc. biol.*, **135**, 459–62 (1941)
19. Bloomer, W. E., Harrison, W., Lindskog, G. F., and Liebow, A. A., *Am. J. Physiol.*, **157**, 317–28 (1949)
20. Bohr, C., *Skand. Arch. Physiol.*, **22**, 221–80 (1909)
21. Bøje, O., *Arbeitsphysiol.*, **7**, 157–66 (1934)
22. Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S., *J. Clin. Invest.*, **28**, 1138–43 (1949)
23. Borden, C. W., Wilson, R. H., Ebert, R. V., and Wells, H. S., *Am. J. Med.*, **8**, 701–9 (1950)
24. Bradford, J. R., and Dean, H. P., *J. Physiol. (London)*, **16**, 34–96 (1894)
25. Bruner, H. D., and Schmidt, C. F., *Am. J. Physiol.*, **148**, 648–66 (1947)
26. Burton, A. C., *Am. J. Physiol.*, **164**, 319–29 (1951)
27. Burton, A. C., *Visceral Circulation*, 70–84 (Little, Brown & Co., Boston, Mass., 278 pp., 1953)
28. Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J., *Bull. Johns Hopkins Hosp.*, **88**, 20–37 (1951)
29. Carroll, D., Cohn, J. E., and Riley, R. L., *J. Clin. Invest.*, **32**, 510–25 (1953)
30. Churchill, E. D., and Cope, O., *J. Exptl. Med.*, **49**, 531–37 (1929)
31. Cockett, F. B., *Visceral Circulation*, 37–43 (Little, Brown & Co., Boston, Mass., 278 pp., 1953)
32. Cockett, F. B., and Vass, C. C. N., *Thorax*, **6**, 268–75 (1951)
33. Cohn, J. E., Carroll, D. G., Armstrong, B., Shepard, R. H., and Riley, R. L., *J. Appl. Physiol.* (In press)
34. Cournand, A., *Bull. N.Y. Acad. Med.*, **23**, 27–50 (1947)
35. Cournand, A., *Circulation*, **2**, 641–57 (1950)
36. Cournand, A., *Harvey Lectures, Ser. 46*, 68–97 (1952)
37. Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J., *Am. J. Physiol.*, **150**, 267–71 (1947)
38. Cournand, A., Riley, R. L., Austrian, R., Donald, K. W., and Himmelstein, A., *Trans. Assoc. Am. Physicians*, **62**, 134–47 (1949)
39. Cournand, A., Riley, R. L., Himmelstein, A., and Austrian, R., *J. Thoracic Surg.*, **19**, 80–116 (1950)
40. Crenshaw, G. L., and Rowles, D. F., *J. Thoracic Surg.*, **24**, 398–408 (1952)

41. Cudkowicz, L., *Thorax*, **7**, 270–76 (1952)
42. Cudkowicz, L., and Armstrong, J. B., *Thorax*, **6**, 343–58 (1951)
43. Cudkowicz, L., and Armstrong, J. B., *Thorax*, **8**, 46–58 (1953)
44. Dalton, J. C., *Doctrines of the Circulation* (Henry C. Lea's Son and Co., Philadelphia, Penna., 296 pp., 1884)
45. Daly, I. de B., *Physiol. Revs.*, **13**, 149–84 (1933)
46. Daly, I. de B., *Harvey Lectures, Ser.*, *31*, 235–55 (1936)
47. Daly, I. de B., Duke, H., Hebb, C. O., and Weatherall, J., *Quart. J. Exptl. Physiol.*, **34**, 285–313 (1948)
48. Daly, I. de B., Duke, H. N., Linzell, J. L., and Weatherall, J., *Quart. J. Exptl. Physiol.*, **37**, 149–62 (1952)
49. Daly, I. de B., and Hebb, C. O., *Quart. J. Exptl. Physiol.*, **37**, 19–43 (1952)
50. Daly, I. de B., Ludány, G., Todd, A., and Verney, E. B., *Quart. J. Exptl. Physiol.* **27**, 123–46 (1938)
51. Dawes, G. S., *Brit. Med. Bull.*, **8**, 324–30 (1952)
52. Denst, J., Hurst, A., and Dressler, S. H., *Am. Rev. Tuberc.*, **64**, 489–98 (1951)
53. Deuchar, D. C., and Knebel, R., *Brit. Heart J.*, **14**, 225–49 (1952)
54. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K., *J. Clin. Invest.*, **29**, 602–13 (1950)
55. Dexter, L., Lewis, B. M., Haynes, F. W., Gorlin, R., and Houssay, H. E. J., *Bull. New Engl. Med. Center*, **14**, 69–80 (1952)
56. Dexter, L., Whittenberger, J. L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Spiegl, R. J., *Trans. Assoc. Am. Physicians*, **64**, 226–35 (1951)
57. Dirken, M. N. J., and Heemstra, H., *Quart. J. Exptl. Physiol.*, **34**, 193–211 (1948)
58. Dirken, M. N. J., and Heemstra, H., *Quart. J. Exptl. Physiol.*, **34**, 213–26 (1948)
59. Dirken, M. N. J., and Heemstra, H., *Quart. J. Exptl. Physiol.*, **34**, 227–41 (1948)
60. Donald, K. W., Renzetti, A., Riley, R. L., and Cournand, A., *J. Appl. Physiol.*, **4**, 497–525 (1952)
61. Douglas, C. G., and Haldane, J. S., *J. Physiol. (London)*, **44**, 305–54 (1912)
62. Dow, J. W., and Gorlin, R., *Federation Proc.*, **9**, 33 (1950)
63. Doyle, J. T., Lee, R. A., and Kelley, E. B., *Am. Heart J.*, **44**, 565–70 (1952)
64. Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V., *J. Clin. Invest.*, **30**, 345–52 (1951)
65. Doyle, J. T., Wilson, J. S., and Warren, J. V., *Circulation*, **5**, 263–70 (1952)
66. Dresdale, D. T., Schultz, M., and Michtom, R. J., *Am. J. Med.*, **11**, 686–705 (1951)
67. Dressler, S. H., Slonim, N. B., Balchum, O. J., Bronfin, G. J., and Ravin, A., *J. Clin. Invest.*, **31**, 807–14 (1952)
68. Dressler, W., *Am. J. Med. Sci.*, **223**, 131–43 (1952)
69. Duke, H. N., *Quart. J. Exptl. Physiol.*, **35**, 25–37 (1950)
70. Duke, H. N., *Quart. J. Exptl. Physiol.*, **36**, 75–88 (1951)
71. Duke, H. N., and Killick, E. M., *J. Physiol. (London)*, **117**, 303–16 (1952)
72. Ebert, R. V., Borden, C. W., Wells, H. S., and Wilson, R. H., *J. Clin. Invest.*, **28**, 1134–37 (1949)
73. Edwards, J. E., and Burchell, H. B., *Arch. Internal Med.*, **87**, 372–78 (1951)
74. Edwards, W. S., *Am. J. Physiol.*, **167**, 756–62 (1951)
75. Eliasch, H., Wade, G., and Werkö, L., *Circulation*, **5**, 271–78 1(952)
76. Ellis, F. H., Jr., Grindlay, J. H., and Edwards, J. E., *Surgery*, **30**, 810–26 (1951)

77. Ellis, F. H., Jr., Grindlay, J. H., and Edwards, J. E., *Surgery*, **31**, 167–79 (1952)
78. Ellis, F. H., Jr., Grindlay, J. H., and Edwards, J. E., *J. Thoracic Surg.*, **25**, 358–65 (1953)
79. Ellis, L. B. *et al.*, *Arch. Internal Med.*, **88**, 515–31 (1951)
80. von Euler, U.S., and Liljestrand, G., *Acta Physiol. Scand.*, **12**, 301–20 (1946)
81. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr., and Cournand, A., *Circulation*, **1**, 161–86 (1950)
82. Filley, G. (Personal communication)
83. Fishman, A. P., McClement, J., Himmelstein, A., and Cournand, A., *J. Clin. Invest.*, **31**, 770–81 (1952)
84. Forbes, W. H., Sargent, F., and Roughton, F. J. W., *Am. J. Physiol.*, **143**, 594–608 (1945)
85. Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J., *J. Clin. Invest.*, **29**, 1387–96 (1950)
86. Fowler, N. O., Jr., Westcott, R. N., and Scott, R. C., *J. Clin. Invest.*, **31**, 72–79 (1952)
87. Fowler, N. O., Westcott, R. N., Scott, R. C., and McGuire, J., *J. Clin. Invest.*, **30**, 517–24 (1951)
88. Frisk, A. R., Hammarström, S., Lagerlöf, H., Werkö, L., Björkenheim, G., Holmgren, A., and Larsson, Y., *Am. J. Med.*, **5**, 807–14 (1948)
89. Gaddum, J. H., and Holtz, P., *J. Physiol. (London)*, **77**, 139–58 (1933)
90. Giampalmo, A., *Acta Med. Scand.*, Suppl. 248, 1–67 (1950)
91. Gibbon, J. H., Jr., Hopkinson, M., and Churchill, E. D., *J. Clin. Invest.*, **11**, 543–53 (1932)
92. Gilmore, H. R., Kopelman, H., McMichael, J., and Milne, I. G., *Lancet*, **II**, 898–902 (1952)
93. Gilroy, J. C., Wilson, V. H., and Marchand, P., *Thorax*, **6**, 137–44 (1951)
94. Gobbel, W. G., Gordon, J., and Digman, G. J., *J. Thoracic Surg.*, **21**, 385–90 (1951)
95. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G., and Roh, C. E., *Am. J. Med.*, **5**, 792–806 (1948)
96. Gordon, D. B., Flasher, J., and Drury, D. R., *Am. J. Physiol.*, **173**, 275–81 (1953)
97. Gray, F. D., Jr., Lurie, P. R., and Whittemore, R., *Yale J. Biol. and Med.*, **23**, 380–89 (1951)
98. Greene, D. G., and Bunnell, I. L., *J. Clin. Invest.*, **29**, 818–19 (1950)
99. Haddy, F. J., Adlen, J. F., Ferrin, A. L., Hannon, D. W., Adams, W. L., and Baronofsky, I. D., *Circulation Research*, **1**, 157–61 (1953)
100. Haddy, F. J., and Campbell, G. S., *Am. J. Physiol.*, **172**, 747–51 (1953)
101. Haddy, F. J., Campbell, G. S., Adams, W. L., and Visscher, M. B., *Am. J. Physiol.*, **158**, 89–95 (1949)
102. Hall, P. W., III, *Circulation Research*, **1**, 238–41 (1953)
103. Halmágyi, D., Felkai, B., Iványi, J., Zsótér, T., Tényi, M., and Szücs, Z., *Brit. Heart J.*, **15**, 15–24 (1953)
104. Halmágyi, D., Iványi, J., Felkai, B., Zsóter, T., Tényi, M., and Szücs, Z., *Scand. J. Clin. & Lab. Invest.*, **5**, 85–89 (1953)
105. Hamilton, W. F., *J. Allergy*, **22**, 397–410 (1951)
106. Hamilton, W. F., Woodbury, R. A., and Vogt, E., *Am. J. Physiol.*, **125**, 130–41 (1939)

107. Hanlon, C. R., Scott, H. W., Jr., and Olson, B. J., *Surgery*, **28**, 209–24 (1950)
108. Hartridge, H., *J. Physiol. (London)*, **45**, 170–81 (1912)
109. Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A., *Am. J. Med.*, **10**, 719–38 (1951)
110. Harvey, R. M., Ferrer, M. I., and Cournand, A., *Circulation*, **7**, 932–40 (1953)
111. Hatch, T. F., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 1–8 (1952)
112. Hebb, C. O., and Nimmo-Smith, R. H., *Quart. J. Exptl. Physiol.*, **34**, 159–64 (1948)
113. Hellems, H. K., Haynes, F. W., and Dexter, L., *J. Appl. Physiol.*, **2**, 24–29 (1949)
114. Hellems, H. K., Haynes, F. W., Dexter, L., and Kinney, T. D., *Am. J. Physiol.*, **155**, 98–105 (1948)
115. Henry, E. W., *Brit. Heart J.*, **14**, 406–12 (1952)
116. Hickam, J. B., *Am. Heart J.*, **38**, 801–12 (1949)
117. Hickam, J. B., and Cargill, W. H., *J. Clin. Invest.*, **27**, 10–23 (1948)
118. Hilton, S. M., *J. Physiol. (London)*, **120**, 230–45 (1953)
119. Howarth, S., and Lowe, J. B., *Brit. Heart J.*, **15**, 47–54 (1953)
120. Hürlimann, A., and Wiggers, C. J., *Circulation Research*, **1**, 230–37 (1953)
121. Krogh, A., *Skand. Arch. Physiol.*, **23**, 248–78 (1910)
122. Krogh, A., and Krogh, M., *Skand. Arch. Physiol.*, **23**, 179–92 (1910)
123. Krogh, A., and Krogh, M., *Skand. Arch. Physiol.*, **23**, 236–47 (1910)
124. Krogh, M., *J. Physiol. (London)*, **49**, 271–300 (1915)
125. Lagerlöf, H., Eliasch, H., Werkö, L., and Berglund, E., *Scand. J. Clin. & Lab. Invest.*, **3**, 85–91 (1951)
126. Lagerlöf, H., and Werkö, L., *Scand. J. Clin. & Lab. Invest.*, **1**, 147–58 (1949)
127. Larsell, O., and Dow, R. S., *Am. J. Anat.*, **52**, 125–46 (1933)
128. Lemoine, J. M., *La thrombose de l'artère bronchique, cause de dilatation bronchique, chronique de l'adulte*, (Doctoral thesis, University of Paris, Paris, France, 189 pp., 1936)
129. Lewis, B. M., and Gorlin, R., *Am. J. Physiol.*, **170**, 574–87 (1952)
130. Liebow, A. A., Hales, M. R., Bloomer, W. E., Harrison, W., and Lindskog, G. E., *Am. J. Pathol.*, **26**, 177–95 (1950)
131. Liebow, A. A., Hales, M. R., Harrison, W., Bloomer, W. E., and Lindskog, G. E., *Yale J. Biol. and Med.*, **22**, 637–50 (1950)
132. Liebow, A. A., Hales, M. R., and Lindskog, G. E., *Am. J. Pathol.*, **25**, 211–31 (1949)
133. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D., and Franke, R. E., *Am. J. Physiol.*, **147**, 199–216 (1946)
134. Liljestrand, G., *Arch. Internal Med.*, **81**, 162–72 (1948)
135. Logaras, G., *Acta Physiol. Scand.*, **14**, 120–35 (1947)
136. McCann, W. S., *Am. J. Med.*, **8**, 62–70 (1950)
137. McClement, J. H., Renzetti, A. D., Carroll, D., Himmelstein, A., and Cournand, A., *Am. Rev. Tuberc.*, **64**, 583–601 (1951)
138. McKeown, F., *Brit. Heart J.*, **14**, 25–32 (1952)
139. Marchand, P., Gilroy, J. C., and Wilson, V. H., *Thorax*, **5**, 207–21 (1950)
140. Miller, W. S., *The Lung* (Charles C Thomas, Publisher, Springfield, Ill., 222 pp., 1947)
141. Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Dresdale, D., *Am. J. Physiol.*, **150**, 315–20 (1947)

142. Mounsey, J. P. D., Ritzman, L. W., Selverston, N. J., Briscoe, W. A., and Mc-Lemore, G. A., *Brit. Heart J.*, **14**, 153–62 (1952)
143. Nichol, J., Girling, F., Jerrard, W., Claxton, E. B., and Burton, A. C., *Am. J. Physiol.*, **164**, 330–44 (1951)
144. Nisell, O., *Acta Physiol. Scand.*, **16**, 121–27 (1949)
145. Nisell, O., *Acta Physiol. Scand.*, Suppl. 73 (1950)
146. Nisell, O., *Acta Physiol. Scand.*, **23**, 85–90 (1951)
147. Nisell, O., *Acta Physiol. Scand.*, **23**, 352–60 (1951)
148. Nisell, O., *Acta Physiol. Scand.*, **23**, 361–74 (1951)
149. Olson, B. J., Scott, H. W., Jr., Hanlon, C. R., and Mattern, C. F. T., *Am. Rev. Tuberc.*, **65**, 48–63 (1952)
150. Pappenheimer, J. R., Renkin, E. W., and Borrero, L. M., *Am. J. Physiol.*, **167**, 13–46 (1951)
151. Parin, V. V., *Am. J. Med. Sci.*, **214**, 167–76 (1947)
152. Pearce, J. W., and Whitteridge, D., *Quart. J. Exptl. Physiol.*, **36**, 177–88 (1951)
153. Peters, R. M., and Roos, A., *Am. J. Physiol.*, **171**, 250–55 (1952)
154. Peters, R. M., and Roos, A., *J. Thoracic Surg.*, **24**, 389–97 (1952)
155. Prinzmetal, M., Ornitz, E. M., Jr., Simkin, B., and Bergman, H. C., *Am. J. Physiol.*, **152**, 48–52 (1948)
156. Rahn, H., and Bahnson, H. T., *Federation Proc.*, **9**, 102–3 (1950)
157. Rahn, H., Stroud, R. C., and Tobin, C. E., *Proc. Soc. Exptl. Biol. Med.*, **80**, 239–41 (1952)
158. Riley, R. L., *Federation Proc.*, **11**, 129 (1952)
159. Riley, R. L., and Cournand, A., *J. Appl. Physiol.*, **4**, 77–101 (1951)
160. Riley, R. L., Cournand, A., and Donald, K. W., *J. Appl. Physiol.*, **4**, 102–20 (1951)
161. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A., *Am. J. Physiol.*, **152**, 372–82 (1948)
162. Riley, R. L., Lilienthal, J. L., Jr., Proemmel, D. D., and Franke, R. E., *Am. J. Physiol.*, **147**, 191–98 (1946)
163. Riley, R. L., Riley, M. C., and Hill, H. McD., *Bull. Johns Hopkins Hosp.*, **91**, 345–70 (1952)
164. Riley, R. L., Shepard, R. H., Cohn, J. E., Carroll, D. G., and Armstrong, B., *J. Appl. Physiol.* (In press)
165. Roughton, F. J. W., *Am. J. Physiol.*, **143**, 609–20 (1945)
166. Roughton, F. J. W., *Am. J. Physiol.*, **143**, 621–33 (1945)
167. Sarnoff, S. J., and Berglund, E., *Am. J. Physiol.*, **170**, 588–600 (1952)
168. Sarnoff, S. J., and Berglund, E., *Am. J. Physiol.*, **171**, 238–44 (1952)
169. Sarnoff, S. J., Berglund, E., and Sarnoff, L. C., *J. Appl. Physiol.*, **5**, 367–74 (1953)
170. Sarnoff, S. J., and Sarnoff, L. C., *Circulation*, **6**, 51–62 (1952)
171. Schwiegk, H., *Pflügers Arch. ges. Physiol.*, **236**, 206–19 (1935)
172. Scott, H. W., Jr., Hanlon, C. R., and Olson, B. J., *J. Thoracic Surg.*, **20**, 761–74 (1950)
173. Sjöstrand, T., *Physiol. Rev.*, **33**, 202–28 (1953)
174. Steinberg, I., McCoy, H. I., and Dotter, C. T., *Am. Rev. Tuberc.*, **62**, 353–59 (1950)
175. Stroud, R. C., and Rahn, H., *Am. J. Physiol.*, **172**, 211–20 (1953)
176. Tigerstedt, R., *Ergeb. Physiol.*, **2** (II), 528–84 (1903)

177. Tobin, C. E., and Zariquiey, M. O., *Proc. Soc. Exptl. Biol. Med.*, **75**, 827–29 (1950)
178. Viar, W. N., and Harrison, T. R., *Circulation*, **5**, 1–11 (1952)
179. Wearn, J. T., Ernstene, A. C., Bromer, A. W., Barr, J. S., German, W. J., and Zschiesche, L. J., *Am. J. Physiol.*, **109**, 236–56 (1934)
180. Weissel, W., Salzmann, F., and Vetter, H., *Brit. Heart J.*, **14**, 47–52 (1952)
181. Werkö, L., Frisk, A. R., Wade, G., and Eliasch, H., *Lancet*, **II**, 470–72 (1951)
182. Werkö, L., and Lagerlöf, H., *Scand. J. Clin. & Lab. Invest.*, **2**, 181–97 (1950)
183. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J., *J. Clin. Invest.*, **30**, 957–70 (1951)
184. Whitteridge, D., *Physiol. Rev.*, **30**, 475–86 (1950)
185. Witham, A. C., and Fleming, J. W., *J. Clin. Invest.*, **30**, 707–17 (1951)
186. Witham, A. C., Fleming, J. W., and Bloom, W. L., *J. Clin. Invest.*, **30**, 897–902 (1951)
187. Wood, D. A., and Miller, M., *J. Thoracic Surg.*, **7**, 649–70 (1938)
188. Wood, P., *Brit. Med. Bull.*, **8**, 348–53 (1952)
189. Yu, P. N. G., Lovejoy, F. W., Jr., Joos, H. A., Nye, R. E., Jr., and McCann, W. S., *J. Clin. Invest.*, **32**, 130–37 (1953)
190. Zimmerman, H. A., *Diseases of the Chest*, **20**, 46–74 (1951)

PHYSICAL AGENTS AND TRAUMA[1,2]

MECHANISMS AND THERAPY OF TRAUMATIC SHOCK

By R. Carl Millican and Sanford M. Rosenthal

Section of Pharmacology and Toxicology of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland

This review will emphasize the recent experimental work in the field of traumatic shock, including injury produced by burns, trauma, and hemorrhage. There are certain limitations to the application to man of results obtained upon laboratory animals, particularly in the transfer of quantitative data. However, with improvement in techniques for studying shock, there is increasing agreement in results from various species, and it is believed that solutions to the major problems in this field will originate in the laboratory.

This review will be limited to the acute episode of traumatic shock and will be restricted to the literature since 1951, not covered in the *Annual Review of Medicine* by Evans (45a), Behnke (14a), and Harkins (81a). Recent symposia on this subject include: *Symposium on Burns* (178), *Symposium on Shock* (179), *Shock Syndrome* (165), and *Shock and Circulatory Homeostasis* (164). Of additional interest is the report of Grant & Reeve (71) on the clinical and biochemical effects of wound shock in man.

MECHANISMS

Fluid and Electrolyte Disturbances

Recent reviews on this subject may be found by Randall (153) and Overman (146). The original concept of Blalock that a loss of approximately half the blood volume will produce fatal shock and that this volume of fluid accumulates locally in traumatized areas in traumatic shock, or escapes from the body in hemorrhage, has been generally confirmed. Under experimental conditions, the accumulation of fluid in areas of trauma is rapid, reaching a maximum in 2 to 4 hr. Fuhrman & Crismon (66, 67) analyzed the fluid and electrolyte changes in injured muscle of rats and rabbits and confirmed previous observations of Tabor & Rosenthal (180) that the injured cells lose potassium and take up sodium so that the total sodium accumulation is greater than that of water. Application of casts reduced the swelling but did not lessen the entrance of sodium into the cells. Koletsky & Gustafson (99),

---

[1] The survey of the literature to which this review pertains was completed in July, 1953.

[2] The following abbreviations are used in this review: ACTH (adrenocorticotropin); DOCA (desoxycorticosterone); MFG (modified fluid gelatin); OPG (oxypolygelatin); PVP (polyvinylpyrrolidone); Tm$_{PAH}$ (tubular maximum); VDM (vasodepressor material); VEM (vasoexciter material).

as well as Rhinelander, Langohr & Cope (159) had previously shown the relative ineffectiveness of application of casts in preventing fluid extravasation. Winfield, Fox & Mersheimer (195) found a similar Na-K exchange in human muscles injured during operative procedures. Calvi (28) found in hemorrhage an increase in liver K accompanying a decrease in muscle K. Bekaert & Demeester (15) observed no marked changes in the Na or K content of cerebrospinal fluid taken from dogs in traumatic shock.

Lemley & Meneely (105) found a decrease of intracellular water associated with increases of total and extracellular water in anoxic heart muscle, but not for skeletal muscle. Fogelman, Montgomery & Moyer (48) measured the transcapillary movement of water following hemorrhage in dogs and found it reduced from 72 per cent blood water per minute to 39 per cent, signifying a decreased functional capillary area. The enormously rapid movement of water was emphasized.

The development of quantitative techniques permitted Tabor, Rosenthal & Millican (181) to measure the distribution of fluid in untreated and treated mice following tourniquet trauma. Dehydration of the uninjured tissues was of a similar extent in the viscera and the uninjured upper half of the body. Administered fluids accumulated in the injured areas as increased swelling so that even with large amounts of saline (18 per cent of body weight), none was recovered in the uninjured tissues beyond that which corrected the dehydration. Thus, after 2 hr. nearly all of the administered fluid could be recovered in the injured areas.

Measurable degrees of alteration in the electrolyte pattern in the uninjured tissues as a necessary sequence to these electrolyte shifts or as a result of the anoxia which accompanies shock have been found by Fox & Keston (53), Fox, Lasker & Winfield (55), and by Darrow & Engel (38).

Reinhardt (156) and Shrewsbury & Reinhardt (168) studied the partition of infused fluids (50 per cent body weight in 4 to 6 hr.) between lymph and urine in the rat and showed that lymph flow (and extracellular fluid volume) was more effectively expanded by saline solutions, dextrose solutions being more rapidly excreted. Wasserman & Mayerson (188) measured the extracellular fluid expansion following large volumes of saline and concluded that volumes exceeding three-fourths the plasma volume were not desirable, but it must be pointed out that this relationship was established in normal and not dehydrated animals.

COLLOID STUDIES

The studies of Wasserman & Mayerson (187), of Forker, Chaikoff & Reinhardt (49), and of Abdou, Reinhardt & Tarver (1), form an important contribution to the relation of plasma proteins to the extracellular fluid and lymph. Quantitative data by the first-named authors (187) revealed that intravenously injected albumin (I^{131} labeled) attained concentrations in the lymph equal to those in the plasma within 7 to 13 hr., so that every 20 hr. the entire plasma albumin has circulated through the extracellular spaces

and lymph. Studies with dextran by Grotte, Knutson & Bollman (77) in rats and of Wasserman & Mayerson (189) in dogs demonstrated a dynamic equilibrium with the extracellular fluid, similar to plasma proteins. The plasma proteins must thus be considered in active equilibrium with the entire extracellular fluid, and not maintained within the vascular bed.

Harroun, Smyth & Levey (82) and Calvin (29) presented evidence that saline infusions mobilized proteins from cellular sources but Wasserman & Mayerson (188) showed that this is a mobilization of "plasma" proteins from the extravascular spaces. This is pertinent to the older concept that saline infusions cause a "loss" of plasma proteins in the tissues, but the significance of this must be reevaluated in the light of the normally existing rapid circulation of these proteins.

These observations lead to a discussion of the following questions: (a) To what extent are protein infusions superior to electrolyte solutions in fluid "loss" into traumatized areas? (b) Do proteins pass more rapidly into traumatized areas than into normal extracellular spaces? (c) How active is circulation of fluids, electrolytes, and proteins in the traumatized tissues and edema fluid? (d) What is the role of protein loss in the circulatory collapse in shock? (e) What are the relative merits of colloid and electrolyte solutions in the therapy of shock? Experimental evidence at present does not permit definitive answers to all of these questions, and reference will be made here only to the recent literature. Questions (d) and (e) will be discussed in other sections of this review.

The earlier experiments of Fine & Seligman (46) with I^{131} tagged albumin indicated that proteins do pass rapidly into traumatized tissues, but no large increases into nontraumatized tissues in the shocked animal were found. The electrophoretic studies of Moore and co-workers (125, 126, 127) in mice and dogs and Westphal, Priest & Stets (191) in rabbits indicated that significant amounts of albumin appear in the area of injury accompanied by a decrease of albumin in the serum. Bollman (19), after infusion of dextran into rabbits, found an equilibrium between plasma and lymph dextran similar to the above results with albumin. Following hemorrhage the restoration of plasma volume was similar with dextran and saline when they were administered prior to hemorrhage. Tabor, Rosenthal & Millican (123, 181) found no difference in the rate or total amount of fluid accumulation in the injured areas when plasma or saline was injected into mice in tourniquet shock. Since the plasma protein levels were widely different (123), it would seem that the ability of traumatized tissues to take up fluids is not markedly influenced by this factor.

Local cooling of injured tissues has been shown to have a pronounced effect on the extent of swelling and the survival of the individual [Allen & Safford (2); Langohr et al. (103)]. Moore & Worf (128) showed electrophoretically that cooling reduces the amount of plasma proteins in the injured tissues by one-third. Westphal and co-workers (190, 191) observed that the azorubin-binding capacity of serum albumin in rats and rabbits was de-

creased in tourniquet shock; the significance of this phenomenon remains to be established.

Courtice & Steinbeck (37a) have demonstrated that intraperitoneally administered whole blood, plasma, and saline are absorbed through the diaphragmatic peritoneum into the underlying lymphatics and enter the venous circulation by way of the right lymphatic duct (primarily) and the thoracic duct.

CIRCULATORY DISTURBANCES

Additional evidence has been presented by Gibson et al. (68), Delormé, Mukherjee & Rowlands (42) and Delormé (41) that stagnation of the circulatory system exists in shock with actual "trapping" or removal of red cells from the general circulation. "Trapping" sites have been indicated to be the portal area by Frank et al. (64) (confirming earlier workers) and muscle, liver, and intestine by Delormé (41). The role that this segregation of blood within the vascular bed plays in shock has not been settled. Frank et al. (59) found that shunting of blood away from the portal area in Eck-fistula dogs did not affect survival. Zanetti (197) has concluded that elevated portal pressure was not an initiating factor in shock. In addition to the "trapping" of blood in shock, Delormé, Mukherjee & Rowlands (42) showed that hemorrhage also produces a release of red cells sequestered in some blood depots.

The significance of segregated erythrocytes, "sludged blood," in shock likewise awaits clarification. Quantitative data on the circulatory effects of sludging may reveal important information. The pioneer work on sludging was done by Knisely who has recently reviewed the subject (98). A critical review is presented by Lutz (109).

Millican et al. (124) studied the hemodynamic responses to various types of therapy in burn and tourniquet shock in mice and found that the early responses could be misleading as criteria of survival. Plasma protein concentration bore no relation to survival; "bleeding volume" and hematocrit were reliable only if repeated determinations were made over a period of hours.

Friedman and co-workers (65) found the portal pressure fell to 60 per cent of its original value after hemorrhagic shock in rats, associated with narrowing of the hepatic venules and sinusoids. Transfusion corrected these changes without necessarily producing survival. These authors found opposite changes in the dog (64). Veal, Russell & Ashburn (186) confirmed the work of Wiggers that the decline in coronary blood pressure parallels the peripheral fall. Case and co-workers (32) likewise implicated coronary circulation. In a standardized 20 per cent surface burn in dogs Salzberg & Evans (161) observed decreases in plasma and red cell volumes at 6 hr. which had returned to normal by 27 hr. after injury.

The marked reduction in renal blood flow which occurs in shock was found by Brandfonbrenner & Geller (22) to be in part prevented by N-(2-chloroethyl) dibenzylamine (Dibenamine), suggesting a role of the sympa·

thetic nervous system. Block, Wakim & Mann (17) demonstrated (pathologically) degenerative changes in the renal cortex, following severe hemorrhage in rats and dogs (18), while Mukherjee (139) found these same changes where present in all parts of the renal tubules with the glomeruli unaffected following tourniquet shock in dogs.

In respiratory burns in dogs accompanied by pulmonary congestion and edema, Aviado & Schmidt (6) observed that the factors contributory to pulmonary congestion were: an increased lung blood volume, decreased pulmonary flow, increased arterial pressure with a normal left atrial pressure, and the presence of a histologically demonstrable "cuffing" of pulmonary veins with edema fluid.

Kovach & Takacs (100) reported, in dogs subjected to fatal hemorrhage or tourniquet trauma, a decreased vascular responsiveness during shock (as measured by blood pressure response to epinephrine and electrical stimulation of the splanchnic nerve) which was restored to normal by infusions of blood or saline.

Metabolic Disturbances

Metabolic rate.—The basal metabolic rate of patients following thermal injury was found to be elevated for long intervals after injury by Cope *et al.* (34). However, thyroid function appeared to be normal on the basis of thyroid function studies. De Gribble & Peters (39), in a preliminary report, indicated that the urinary nitrogen loss following burns in rats was largely abolished after thyroidectomy.

Liver.—James, Purnell & Evans (92, 93) observed that patients sustaining third degree burn injury manifested soon after injury an elevated fecal urobilinogen, as a result of the hemolysis of erythrocytes at the time of burn. Urinary urobilinogen began to rise about the third day and remained elevated for long periods. Although the latter indicated liver injury, no constant pathological lesions in the liver were demonstrable at death. Frank *et al.* (56) reported that plasma prothrombin activity declines during hemorrhagic shock in dogs and slowly returns to normal after transfusion. Since prothrombin synthesis occurs in liver, the delayed return of plasma prothrombin activity to normal indicated that liver injury persisted long after correction of blood volume deficit. Beck & Linkenheimer (14) reported a marked decrease in the liver nonprotein sulfhydryl concentration. In a reinvestigation of the oxygen consumption of liver slices from shocked animals, Cook, Jensen & South (33) found a 25 per cent increase, which these workers considered as suggestive of a chemical factor accelerating cell oxidation. In hemorrhagic shock in dogs, Kimura, Iijima & Hara (95, 96, 97) reported decreases in the amount of Fe, Cu, Co, Ni, Mn, and Mg of the liver and no changes in the spleen Fe and Cu content. Liver Fe and Cu decreases occurred with the onset of shock and not with the hemorrhage. Although no determinations of the total ferritin content were made, they did report a striking decrease in shock in the Fe content of ferritin, indicating that during shock

Fe is liberated, in part, from ferritin. Venous serum Fe decreased while serum Mg increased. Similar increases in serum Mg were observed by Terkildsen (182).

Cardiac muscle.—Burdette (27) reported an increase in the oxygen uptake of cardiac muscle slices removed from shocked rats soon after trauma. Slices removed 4 hr. after trauma showed a decrease.

Carbohydrate metabolism.—The recent review of Engel (44) summarizes the previous experimental work on this subject. The effects of nucleotide shock on carbohydrate metabolism were described by Stoner, Threlfall & Green (174, 184). A hyperglycemia occurred (from glycogen conversion) which persisted after carbohydrate mobilization since glucose utilization in shock was decreased. Tissue citrate was also shown to increase. Immediately preceding death the blood glucose level fell rapidly and signs of anerobic glycolysis appeared. However, elevated tissue glucose concentrations persisted until death. Changes in blood glucose, lactate, and pyruvate were reported for ischemic shock. In shock in rats, Kovach et al. (102) reported decreases in glucose uptake by diaphragms and in the hexokinase activity of muscle extracts of intact animals. Adrenalectomy or hypophysectomy abolished these effects. Cordier et al. (35) found a marked decrease in phosphorylation of glycogen by homogenates of liver from shocked rats; Moyson & Gavosto (138) reported changes in the distribution of glucose-6-phosphatase activity of mitochondria, microsomes, and the supernatant in liver homogenates of shocked rats.

Kovach and co-workers (101) demonstrated in injured muscles decreases in the phosphorylation of glycogen which were partially restored by addition of adenylic acid and inorganic phosphate. Hoffmann, Rottino & Albaum (90) found, in patients in shock, that the blood levels of adenosinetriphosphate, adenosinediphosphate, and adenosinemonophosphate were unchanged. However, they did observe in some patients the appearance in the blood of an ultraviolet absorbing material resembling inosine monophosphate. Serum cholinesterase level in dogs was reported by Jacob et al. (91) as unchanged when animals were subjected to hemorrhagic shock.

Rosen & Levenson (159a) studied the nonprotein nitrogen changes in plasma ultrafiltrates of normal and burned rats and found that the increased filterable nitrogen observed after burning consisted largely of urea and free and combined amino nitrogen in their normal ratios.

HUMORAL AND CELLULAR FACTORS

Hormonal effects.—Wight et al. (193) observed a prompt fall in eosinophil counts in burned patients as early as 12 hr. after injury. The degree of fall did not correlate with the extent of the burn except in minor cases. Cordier & Peres (36, 37) reported a decreased glucose absorption from the intestinal tract of animals in shock which could be increased considerably with limited doses of cortisone and desoxycorticosterone derivatives. Munan & Einheber (140), on the basis of the survival rates in burned rats following starvation,

observed that females exhibited a greater resistance than males, suggesting to them that sex-related factors may be operative.

VEM,[2] VDM[3] and their relation to irreversible shock.—No detailed presentation of this proposed mechanism operative in shock will be attempted since excellent summaries have been presented by its proponents, Zweifach (164, 198) and Shorr (166, 179), and also Granick (70). Baez *et al.* (9) presented additional evidence for the participation of a renal factor, presumably VEM, in the maintenance of vascular homeostasis. In rats subjected to hemorrhage or drum trauma, higher mortalities were observed in animals with kidneys removed than in animals with kidneys intact. These data suggested that the kidney contributed a compensatory factor to vascular homeostasis in shock. Since the lowered resistance of nephrectomized animals to shock could be attributed to other factors, specific or nonspecific, Baez and co-workers added "that other principles, such as renin, or as yet unknown factors, may likewise contribute to the adequate functioning of the peripheral vascular tree during stress."

VDM, the humoral factor responsible for depressing the reactivity of capillaries, has been identified as the iron-protein complex, ferritin. In the hypoxia present during prolonged hypotension, the liver activates its ferritin (166), largely present in the oxidized disulfide form, to the reduced sulfhydryl form. With prolonged hypoxia VDM inactivation (oxidation of ferritin) fails. With this failure shock progresses from a reversible to an irreversible state terminating in death. Experiments designed to improve hepatic anoxia in shock, similar to the earlier ones of Frank *et al.* (57, 163), have been reported by Delormé (40) in dogs and by Baez, Zweifach & Shorr (11) in rats. In these, hepatic arterial perfusion produced a marked improvement in survival. These findings are in agreement with the VEM-VDM hypothesis since arterial perfusion would maintain a predominantly aerobic metabolism inhibiting VDM production and assuring its inactivation. Further supportive evidence was the observation by Shorr and co-workers (167) that rats, made resistant to repeated sub-lethal drum trauma, withstood a graded hemorrhage otherwise lethal to control animals and also exhibited enhanced hepatic VDM inactivation.

Other reported experiments do not support the VEM-VDM hypothesis. Frank *et al.* (62) have reported that ferritin has no effect on the blood pressure or survival of hepatectomized nephrectomized dogs in hemorrhagic shock. Hampton, Friedman & Mayerson (80) reported that increasing the liver ferritin concentration or reducing the amount of circulating ferritin by antiserum injection in rats subjected to drum trauma had no demonstrable effect on either the mortality or mean survival time from that observed in control animals. Stopak (175) in our laboratory has demonstrated that intravenous administration of ferritin to mice in shock did not affect significantly either the mortality rate or final mortality when compared with animals receiving no ferritin.

General acceptance of the VEM-VDM mechanism as operative in rever-

sible-irreversible shock awaits further experimental work demonstrating its operation in other experimental animals as well as man. The development of other methods for the estimation of VDM activity than the present qualitative and nonspecific bioassay of the rat mesoappendix is necessary for the design of future definitive experiments.

"Toxic" factors.—In experiments designed to test whether a "toxin" was operative in "irreversible" hemorrhagic shock, Frank and co-workers (61) subjected dogs in "irreversible" shock to peritoneal irrigation and dialysis with the artificial kidney. No evidence was found of a diffusible "toxin" although these procedures did not lower the elevated urea N in the blood. Peritoneal irrigation was beneficial only because of the absorption of the irrigating fluid.

THERAPY OF TRAUMATIC SHOCK[3]

Moyer (136) has presented an analysis of the mortality of burn cases collected from several hospitals in this country similar to the analysis reported by Bull & Squire (26) for burns in England. Saline supplemented by whole blood was the most effective therapy in severe burns (35 to 70 per cent surface area).

FLUIDS AND ELECTROLYTES

The therapeutic value of saline solutions in the treatment of shock has now been generally established. This acceptance of saline in shock treatment has been largely the result of favorable clinical experience in burn shock. However, there is disagreement as to volumes of saline administered in man to be therapeutically effective and also as to the efficacy of saline compared to colloid and whole blood therapy. The formulae for calculating the saline volumes administered in burn shock recommend 4 to 5 per cent of body weight in the case of Evans (45) and Moore (129), or 10 to 15 per cent of body weight in the case of Fox (52), Moyer (134) and Amspacher *et al.* (158). These volumes of saline are usually administered during the first 24 hr. following hospitalization and in conjunction with plasma, whole blood, or other colloid therapy. Such solutions as sodium chloride-acetate or -bicarbonate are administered orally in the absence of vomiting or of deep shock. McCarthy & Newlin (114) in rat experiments have reported more favorable survival response with 1.4 per cent NaCl than with isotonic saline (0.9 per cent NaCl). Apropos of the relative merits of hypertonic and isotonic saline, it remains to be established that giving slightly larger amounts of isotonic saline might have less hazard. Moyer (135) feels that slightly hypotonic solutions are better tolerated when given orally. In burned mice, Millican, Tabor & Rosenthal (123) have found that, on basis of equal volumes, isotonic saline solution (0.15 M) orally was more beneficial than hypotonic solutions (0.075

[3] The term saline refers to all sodium containing solutions of isotonic (or 0.15M) concentration which are used for physiological purposes.

and 0.1 M). Fox *et al.* (54) have reported a "balanced" electrolyte solution for parenteral administration.

Recent experimental work has also demonstrated the therapeutic efficacy of saline solutions in the treatment of shock. In hemorrhaged dogs, Parkins and co-workers (148) found that saline infusions in volumes of 5 to 15 per cent body weight were more effective in mild shock than in shock with prolonged hypotension. In mice Millican, Tabor & Rosenthal (123) found 10 to 15 per cent body weight of saline far more effective than 5 per cent body weight, and death could be prevented even when treatment was delayed 6 hr. In the experiments of McCarthy & Newlin (114) in burned rats and Parkins and co-workers (148) in hemorrhaged dogs, oral saline was ineffective as a result of poor absorption from the gastrointestinal tract; others in mice (123), rats (81), and dogs (137) have not observed this difficulty. Experimental evidence uniformly indicates that glucose in water solutions have little effect on survival (112, 123, 148).

Whole Blood and Plasma

These fluids are generally accepted as the fluids of choice in the treatment of shock from hemorrhage or muscle trauma. The relative merits of whole blood and plasma in the treatment of shock from burns have been reviewed in the *Annual Review of Medicine* by Harkins (81a). Seeley (162) earlier, as well as Veal, Russell & Ashburn (186) recently, recommend intra-arterial therapy as an emergency procedure. Case *et al.* (32) and Smythe *et al.* (171) found no difference between intra-arterial and intravenous therapy. With plasma, and less so with blood, the hazard of virus hepatitis, or homologous serum jaundice, has become increasingly serious with reports by Murphy & Workman (141) and others that ultraviolet irradiation does not completely sterilize plasma contaminated with the hepatitis virus. There is some indication, in the report by Paine & Janeway (147), that human serum albumin is free of the hepatitis virus.

Whole blood and plasma plus saline was found by McCarthy (110) to give the most favorable survival in burned rats. Millican, Tabor & Rosenthal (123) in mice in tourniquet and burn shock demonstrated an increased benefit from colloids (whole blood and plasma) when they are administered over a period of hours as compared to the same amounts administered rapidly. Plasma was more effective than saline when equal volumes were administered over a period of hours thus showing a therapeutic effect from colloids under these conditions; however, no difference was observed when saline was administered in 50 per cent greater volumes. No difference was found between whole blood and plasma in burn and tourniquet shock.

Plasma Expanders

Recent reviews of the literature on plasma expanders have been presented by Baer (7, 8) and Gropper, Raisz & Amspacher (76). The problem of treating mass casualties in a possible atomic bomb attack with inadequate sup-

plies of whole blood and plasma as well as the hazard involved in the use of hepatitis virus-contaminated plasma has stimulated renewed interest in the development of satisfactory plasma expanders. Recent preparations studied have been: dextran, polyvinylpyrrolidone (PVP), gelatin (Knox P-20), modified gelatins [i.e., modified fluid gelatin (MFG), oxypolygelatin (OPG), and plasmoid gelatin], and modified human globin. Reports so far have been most favorable for dextran and PVP.

Physiological effects.—Reactions: The initial clinical trials with dextran in this country were with Swedish dextran. Allergic type reactions were reported by Turner *et al.* (185) and others. These reactions have been rarely encountered with American dextrans. Although both Swedish and American dextrans are antigenic in man, producing skin sensitivity and precipitins (24, 94), and also react serologically with other polysaccharides (87), Heidelberger (88) feels that dextran "need not necessarily have harmful effects when introduced into the animal body." Allergic type reactions to OPG[2] were reported by Higgins *et al.* (89) and Campbell *et al.* (30). Similar reactions to modified human globin were reported by Plough *et al.* (151) as well as red cells and casts in the urine.

Renal and other effects: Reinhold *et al.* (157) reported no changes in liver function tests following dextran and PVP.[3] Fleming, Cargill & Bloom (47) observed no marked changes in renal clearances or in Tm_{PAH}[2] immediately following dextran infusion, but Michie & Ragni (119) observed a depression in Tm_{PAH} after repeated dextran infusions in both normal patients and patients with pre-existing renal disease. MFG,[2] as reported by Michie *et al.* (118), also produced a slight but definite increase in Tm_{PAH}. Marshall and co-workers (115) reported that chronic dextran administration in dogs produced no demonstrable harmful effects except for a decrease in hematocrit volume. Maintenance of plasma volume expansion with dextran has been satisfactory in normovolemic patients [Wilson *et al.* (194); Hammarsten *et al.* (79); Metcalf & Rousselot (117)]. When administered to human patients subjected to experimental hemorrhage as compared to normovolemic subjects plasma volume increase is greater and more sustained with dextran (79), as well as with OPG and MFG (12). Cardiac output increases after dextran (192). Strumia *et al.* (177) report that modified human globin produced significant increases in blood volume, but Berson *et al.* (16) observed only slight but transitory increases.

Use in shock.—Dextran, PVP, and OPG have been reported to be effective in treating clinical shock. Wilson *et al.* (194), as well as Amspacher & Curreri (4) in Korean war wounded, found that dextran produced a prompt return in blood pressure to normal with disappearance of signs of shock in patients suffering from shock attributable to blood loss, trauma, and dehydration. The reports of Higgins *et al.* (89) with OPG and Haynes *et al.* (86) and Arden *et al.* (5) with PVP indicate also that these two agents are very effective for treating clinical shock.

Experimental studies.—Considerable work, most of it with experimental

hemorrhage, has been reported during recent years on the effectiveness of many different expanders in experimental shock. Much effort has been expended in determining the relative effectiveness of many preparations as plasma expanders. However, as comparisons have been made in different animals under different procedures, as well as other variables, it is impossible to state which preparations are superior. In general, most preparations appeared to be effective plasma expanders, differing chiefly in toxicity and average molecular weights.

Experimental hemorrhage.—Previous mention has been made of the studies of dextran distribution in the plasma lymph and urine before and after bleeding in dogs by Wasserman & Mayerson (189). Parkins and co-workers (149) observed in dogs subjected to acute hemorrhage of a mild degree that dextran, OPG, MFG, blood, or saline were all effective in preventing death. After a prolonged hypotension, blood and MFG were superior to dextran and saline. In graded hemorrhage in dogs [Govier & Colovos (69); Hartman & Behrman (85)], higher survivals were observed following treatment with plasmoid gelatin than with gelatin, OPG, or dextran. Gropper *et al.* (75) in dogs and Raisz & Pulaski (152) in rabbits compared dextran and OPG, as well as plasma and saline therapy. In both hemorrhaged dogs and rabbits, survivals with dextran and OPG were comparable to those with plasma and were superior to saline. In dogs, glomerular filtration rate and renal blood flow, which were reduced in shock, were restored to levels observed in plasma-treated animals. Plasma-treated rabbits yielded higher fatal rebleeding volumes than those receiving dextran or OPG although dextran produced the greatest blood volume expansion. Narat, Casella & Cangelosi (142) demonstrated the effectiveness in shock of intraperitoneally administered dextran and PVP and proposed this route of administration as an alternative to intravenous administration. Morrison, Lundy & Essex (130) studied the effects on survival of dextran, PVP and plasmoid gelatin in hemorrhaged rats, guinea pigs, and dogs, and found them to be satisfactory replacement fluids.

Experimental burn shock.—Millican, Stohlman & Mowry (122) demonstrated a toxicity of certain preparations of dextran, PVP, and OPG in shocked mice although these preparations were well tolerated in normal animals. McCarthy & Draheim (113) reported similar adverse effects on survival of burned rats after PVP and OPG. The nature of this toxicity remains to be elucidated. In a later study by McCarthy (110) with more severely burned rats, optimum survival was obtained with therapy combining blood, plasma, and saline. PVP or OPG, combined with saline, gave survivals comparable to plasma-saline combination, although these survivals were inferior to therapy combining blood, plasma, and saline.

Metabolism of plasma expanders.—The disposition of these plasma expanders in the body has been of interest since a significant proportion of the administered materials cannot be accounted for either in the excretions or in the circulating blood. Gray, Siiteri & Pulaski (73) in phlorizinized starved

dogs, Cargill & Bruner (31), as well as Terry & Yuile (183), with dextran tagged with radioactive C^{14}, demonstrated that dextran is metabolized as glucose. In the depancreatized dog, Grotte, Knutson & Bollman (77) did not find dextran converted to glucose in appreciable amounts. Thus, the rate of dextran metabolism does not appear to be very rapid. Some have reported foam-cell storage and other changes in tissues after dextran [Hartman (83, 84); Hartman & Behrman (85); Turner et al. (185)]; others have not [Nelson & Lusky (144); Bull et al. (25); and others]. The recent development of a histochemical method specific for dextran by Friberg, Graf & Aberg (63) and also by Mowry, Longley & Millican (131), has made possible studies of the distribution of dextran within the tissues of rabbits [Persson (150)] and mice [Mowry & Millican (132)]. In mice dextran was distributed in all tissues, particularly in liver cells, renal tubules, and in widely scattered phagocytes composing the reticuloendothelial system. Its presence in the latter cells was still observed months after injection as was previously shown serologically by Bull and co-workers (25).

The fate of the other plasma substitutes is not as clear. OPG, as reported by Gray & Pulaski (72), is utilized as glucose in the phlorizinized starved animal. Its presence in tissues has been demonstrated by Hartman & Behrman (85) and Mowry & Millican (133). PVP storage in tissues, as indicated by the presence of foam cells, has been demonstrated by Hartman (83, 84), Nelson & Lusky (144), and Narat et al. (142). In studies with PVP tagged with radioactive C^{14} by Steele, Van Slyke & Plazin (172) and Loeffler & Scudder (107), little PVP entered into metabolic channels and was excreted in the urine in a chemically unaltered form. Unexcreted PVP is stored unaltered by phagocytes and localized largely in the skin, liver, spleen, and bone.

DRUGS AND HORMONES

Antibiotics.—Frank and co-workers (60) have shown that in later stages of hemorrhagic shock in dogs, widespread invasion of the tissues by organisms from the gastrointestinal canal can be an important factor in survival, since suitable antibiotic therapy can prevent death in the majority of animals. To assess the role of infection in shock further bacteriologic and antibiotic studies in other species, including man, are urgently needed to establish the universality of these observations. Altemeier et al. (3) demonstrated in shocked dogs that the absorption of antibiotics is delayed. Antibiotic blood concentrations persisted longer and effective antibacterial concentrations were obtained in the area of injury. Lusky & Braun (108) demonstrated that procaine penicillin G of itself was more effective in shocked cats than was procaine hydrochloride, penicillin G, or amorphous aluminum penicillin. No explanation was offered for this unexpected finding. Brooks et al. (23) in dogs and Baxter et al. (13) in swine, under conditions of a high mortality produced by combined radiation injury and thermal burns, brought about the survival of the majority of animals by antibiotic therapy.

ACTH, cortisone, and desoxycorticosterone (DOCA).—ACTH[2] and corti-sone were found by Reichman, You & Sellers (155) and Neal *et al.* (143), to have no effect on survival of burned rats whether they were treated before or after scalding. Pretreatment for one week with DOCA[2] produced an effect on survival comparable to saline therapy. This latter observation was a confirmation of an earlier observation of You & Sellers (196). The demon-strated therapeutic effectiveness of DOCA in pretreated burned animals may be ascribed to its effect of retention of sodium since saline therapy alone in mice and rats is highly effective in promotion of survival after burns. In hemorrhagic shock in dogs, Frank and co-workers (58) reported that corti-sone and ACTH did not prolong the survival time beyond that of control animals. In guinea pigs, Dosne de Pasqualini (43) observed that pretreat-ment with ACTH and cortisone increased survival significantly above that of controls; DOCA had little effect. In rats subjected to intestinal traumati-zation by Smith & D'Amour (170), ACTH and cortisone produced a signifi-cant prolongation of survival time. Halpern, Benacerraf & Briot (78) reported that adrenalectomized rats treated with cortisone and DOCA exhibited increased survival when subjected to hemorrhage or ligation trauma.

Rosenberg *et al.* (160) reported that the use of hyaluronidase in burned mice to speed up subcutaneous absorption of fluids was without danger only when administered away from the site of injury.

Norepinephrine (noradrenalın or arterenol).—Recently Mayer & Ruben (116), Skelton, Mills & Moyer (169), and Miller *et al.* (120) have reported the clinical usefulness of this pressor amine in treating many kinds of shock including those following myocardial infarction, cardiac failure, massive infections, and surgical procedures. Renal studies in normal patients fol-lowing norepinephrine administration, as reported by Skelton, Mills & Moyer (169), revealed decreases of 40 per cent in renal plasma flow and 8 per cent in glomerular filtration rate with no change in Tm_{PAH}. When administered to patients in shock, the usual response was an increase in blood pressure to normal limits. Stohlman (173), in our laboratory, has been unable to demonstrate any effect on survival following administration of this com-pound to mice in shock from burn or tourniquet trauma. It is not surprising that norepinephrine administered in the absence of replacement therapy would be ineffective in experimental shock associated with large fluid loss.

N-(2-chloroethyl) dibenzylamine (Dibenamine).—As reported by Baez, Zweifach & Shorr (10) and Levy, North & Wells (106), N-(2-chloroethyl)-dibenzylamine is effective in rats in experimental shock produced by hemor-rhage or Noble-Collip drum trauma only when animals were pretreated. Zweifach, Baez & Shorr (199) observed that the effectivness of this agent in dogs in hemorrhagic shock was related to absence of vasular decompensa-tion in capillaries, absence of VDM in the blood, and the presence in the liver of an intact VDM inactivation system.

RP-3885 and RP-4560.—These compounds were synthesized by the Rhone-Poulenc Company in France from which laboratories came the

original reports of Bovet and co-workers (20, 21) and Fournel (50, 51) of their therapeutic effect in traumatic shock in mice, rats, guinea pigs, and dogs. RP-3885, ethyl-1-ethane sulfonyl-4-piperazine hydrochloride, was effective in hemorrhage in dogs only when administered shortly before or immediately after hemorrhage. While Strawitz and co-workers (176) have confirmed the effectiveness of RP-3884 in hemorrhage, North & Wells (145) with Noble-Collip drumming of rats, and Millican & Rosenthal (121) with burn or tourniquet shock in mice, were unable to confirm its effectiveness in these latter forms of trauma. Lafontaine (104) found RP-3885 ineffective in burn shock in rats. RP-4560, 10-(-3 dimethylaminopropyl)-3-chlorophenothiazine hydrochloride, like RP-3885 was reported by Fournel (51) to be effective when administered immediately after hemorrhage.

Other drugs.—Greene, Stuart & Joraleman (74) reported that a bacterial polysaccharide, produced under the trade name of Piromen, markedly increased the survival of rats in shock from scalding. This report has not been confirmed by McCarthy (111) in burn-shocked rats or by Millican (121) in burn or tourniquet-shocked mice. Ravich & Revici (154) reported that administration of *n*-butanol in saline or sodium lactate solutions markedly increased survival of mice in burn shock above that of saline or lactate treated controls.

LITERATURE CITED

1. Abdou, I. A., Reinhardt, W. O., and Tarver, H., *J. Biol. Chem.*, **194**, 15–23 (1952)
2. Allen, F. M., and Safford, F. K., *Arch. Surg.*, **61**, 515–23 (1950)
3. Altemeier, W. A., Coith, R. L., and Culbertson, W. R., *Arch. Surg.*, **63**, 403–7 (1951)
4. Amspacher, W. M., and Curreri, A. R., *Arch. Surg.*, **66**, 730–38 (1953)
5. Arden, G. P., Mandow, G. A., and Stoneham, F. J. R., *Lancet*, **I**, 1099–1100 (1951)
6. Aviado, D. M., Jr., and Schmidt, C. F., *Circulation*, **6**, 666–80 (1952)
7. Baer, K. A., "Plasma Substitutes, Except Those Derived from Human Blood—1940–1951," *Annotated Bibliography* (Army Medical Library, Washington, D. C., 1951)
8. Baer, K. A., "Pathology and Physiology of Burns—1942–1951," *Annotated Bibliography* (Armed Forces Medical Library, Washington, D. C., 1951)
9. Baez, S., Zweifach, B. W., Pellon, R., and Shorr, E., *Am. J. Physiol.*, **166**, 658–65 (1951)
10. Baez, S., Zweifach, B. W., and Shorr, E., *Federation Proc.*, **11**, 7 (1952)
11. Baez, S., Zweifach, B. W., and Shorr, E., *Federation Proc.*, **12**, 8 (1953)
12. Barker, H. G., Elder, J. D., Walker, J. M., and Vars, H. M., *Surg. Forum, Proc. 38th Congr. Am. Coll. Surgeons*, 440–44 (1952)
13. Baxter, H., Drummond, J. A., Stephens-Newsham, L. G., and Randall, R. G., *Ann. Surg.*, **137**, 450–55 (1953)
14. Beck, L. V., and Linkenheimer, W., *Proc. Soc. Exptl. Biol. Med.*, **81**, 291–94 (1952)
14a. Behnke, A. R., *Ann. Rev. Med.*, **2**, 243–72 (1951)

15. Bekaert, J., and Demeester, G., *Arch. intern. physiol.*, **59**, 233–35 (1951)
16. Berson, S. A., Yalow, R. S., Post, J., Wisham, L. H., Newerly, K. A., Villazon, M. J., and Vasquez, O. N., *J. Clin. Invest.*, **32**, 22–32 (1953)
17. Block, M. A., Wakim, K. G., and Mann, F. C., *Arch. Pathol.*, **54**, 443–49 (1952)
18. Block, M. A., Wakim, K. G., Mann, F. C., Bennett, W. A., *Surgery*, **32**, 551–80 (1952)
19. Bollman, J. L., *J. Lab. Clin. Med.*, **41**, 421–27 (1953)
20. Bovet, D., Courvoisier, S., Ducrot, R., and Jacob, R., *Compt. rend.*, **227**, 1423–25 (1948)
21. Bovet, D., and Fournel, J., *Proc. Soc. Exptl. Biol. Med.*, **74**, 421–24 (1950)
22. Brandfonbrener, M., and Geller, H. M., *Am. J. Physiol.*, **171**, 482–86 (1952)
23. Brooks, J. W., Evans, E. I., Ham, W. T., Jr., and Reid, J. D., *Ann. Surg.*, **136**, 533–44 (1952)
24. Bryan, G. C., and Scudder, J., *Ann. N. Y. Acad. Sci.*, **55**, 477–78 (1952)
25. Bull, J. P., Ricketts, C., Squire, J. R., Maycock, W. d'A., Spooner, S. J. L., Mollison, P. L., and Paterson, J. C. S., *Lancet*, **I**, 134–43 (1949)
26. Bull, J. P., and Squire, J. R., *Ann. Surg.*, **130**, 160–73 (1949)
27. Burdette, W. J., *Am. J. Physiol.*, **168**, 575–83 (1952)
28. Calvi, L., *Atti. soc. lombarda sci. med. e biol.*, **7**, 226–29 (1952)
29. Calvin, D. B., *Am. J. Physiol.*, **129**, 327–28 (1940)
30. Campbell, D. H., Koepfli, J. B., Pauling, L., Abrahamsen, N., Dandliker, W., Feigen, G. A., Lanni, F., and LeRosen, A., *Texas Repts. Biol. and Med.*, **9**, 235–80 (1951)
31. Cargill, W. H., and Bruner, H. D., *J. Pharmacol. Exptl. Therap.*, **103**, 339 (1951)
32. Case, R. B., Sarnoff, S. J., Waithe, P. E., and Sarnoff, L. C., *J. Am. Med. Assoc.*, **152**, 208–12 (1953)
33. Cook, S. F., Jensen, D., and South, F. E., Jr., *Am. J. Physiol.*, **173**, 253–58 (1953)
34. Cope, O., Nardi, G. L., Quijano, M., Rovit, R. L., Stanbury, J. B., and Wight, A., *Ann. Surg.*, **137**, 165–74 (1953)
35. Cordier, D., Cordier, G., Duveau, A., and Lemarchands, H., *Compt. rend. soc. biol.*, **145**, 1546–48 (1951)
36. Cordier, D., and Peres, G., *Compt. rend. soc. biol.*, **146**, 1195–97 (1952)
37. Cordier, D., and Peres, G., *Rev. can. biol.*, **11**, 221–30 (1952)
37a. Courtice, F. C., and Steinbeck, A. W., *Australian J. Exptl. Biol. Med. Sci.*, **28**, 171–82 (1950); **31**, 215–25 (1953)
38. Darrow, D. C., and Engel, F. L., *Am. J. Physiol.*, **145**, 32–37 (1945)
39. de Gribble, M., and Peters, R. A., *Quart. J. Exptl. Physiol.*, **36**, 119–26 (1951)
40. Delormé, E. J., *Lancet*, **I**, 259–63 (1951)
41. Delormé, E. J., *Quart. J. Exptl. Physiol.*, **38**, 47–54 (1953)
42. Delormé, E. J., Mukherjee, S. R., and Rowlands, S., *Quart. J. Exptl. Physiol.*, **37**, 107–17 (1952)
43. Dosne de Pasqualini, C., *Compt. rend. soc. biol.*, **146**, 139–42 (1952)
44. Engel, F. L., *Ann. N. Y. Acad. Sci.*, **55**, 381–92 (1952)
45. Evans, E. I., *Surg. Gynecol. Obstet.*, **94**, 273–81 (1952)
45a. Evans, E. I., *Ann. Rev. Med.*, **1**, 287–302 (1950)
46. Fine, J., and Seligman, A. M., *J. Clin. Invest.*, **23**, 720–30 (1944)
47. Fleming, J. W., Cargill, W. H., and Bloom, W. L., *Proc. Soc. Exptl. Biol. Med.*, **79**, 604–6 (1952)

48. Fogelman, M. J., Montgomery, P. O'B., and Moyer, C. A., *Am. J. Physiol.*, **169**, 94–101 (1952)

49. Forker, L. L., Chaikoff, I. L., and Reinhardt, W. O., *J. Biol. Chem.*, **197**, 625–36 (1952)

50. Fournel, J., and Dubost, P., *Arch. intern. pharmacodynamie*, **84**, 283–307 (1950)

51. Fournel, J., *Compt. rend. soc. biol.*, **146**, 561–64 (1952)

52. Fox, C. L., Jr., *J. Am. Med. Assoc.*, **124**, 207–12 (1944)

53. Fox, C. L., Jr., and Keston, A. S., *Surg. Gynecol. Obstet.*, **80**, 561–67 (1945)

54. Fox, C. L., Jr., Winfield, J. M., Slobody, L. B., Swindler, C. M., and Lattimer, J. K., *J. Am. Med. Assoc.*, **148**, 827–33 (1952)

55. Fox, C. L., Jr., Lasker, S. E., and Winfield, J. M., *Federation Proc.*, **12**, 45 (1953)

56. Frank, E. D., Frank, H. A., and Fine, J., *Am. J. Physiol.*, **167**, 499–507 (1951)

57. Frank, H. A., Seligman, A. M., and Fine, J., *J. Clin. Invest.*, **25**, 22–29 (1946)

58. Frank, H. A., Fine, J., Friedman, E., Glotzer, P., Jacob, S., and Schwartz, A., *Surg. Forum, Proc. 36th Congr. Am. Coll. Surgeons*, 522–29 (1950)

59. Frank, H. A., Glotzer, P., Jacob, S. W., and Fine, J., *Am. J. Physiol.*, **167**, 508–13 (1951)

60. Frank, H. A., Jacob, S. W., Schweinburg, F. B., Goddard, J., and Fine, J., *Am. J. Physiol.*, **168**, 430–36 (1952)

61. Frank, H. A., Frank, E. D., Jacob, S., Glotzer, P., Persky, L., Friedman, E. W., Schwartz, A., Rutenberg, A. M., Milrod, S., and Fine, J., *Am. J. Physiol.*, **168**, 140–49 (1952)

62. Frank, H. A., Jacob, S., Friedman, E. W., Rutenberg, A. M., Glotzer, P., and Fine, J., *Am. J. Physiol.*, **168**, 150–55 (1952)

63. Friberg, U., Graf, W., and Åberg, B., *Scand. J. Clin. & Lab. Invest.*, **3**, 221–27 (1951)

64. Friedman, E. W., Frank, H. A., and Fine, J., *Ann. Surg.*, **134**, 70–79 (1951)

65. Friedman, E. W., Milrod, S., Frank, H. A., and Fine, J., *Proc. Soc. Exptl. Biol. Med.*, **82**, 636–38 (1953)

66. Fuhrman, F. A., and Crismon, J. M., *Am. J. Physiol.*, **167**, 289–97 (1951)

67. Fuhrman, F. A., and Crismon, J. M., *Am. J. Physiol.*, **166**, 424–37 (1951)

68. Gibson, J. G., Seligman, A. M., Peacock, W. C., Fine, J., Aub, J. C., and Evans, R. D., *J. Clin. Invest.*, **26**, 126–44 (1946)

69. Govier, W. M., and Colovos, G. C., *Ann. N. Y. Acad. Sci.*, **55**, 491–95 (1952)

70. Granick, S., *Physiol. Rev.*, **31**, 489–511 (1951)

71. Grant, R. T., and Reeve, E. B., *Med. Research Council (Brit.), Spec. Rept. Ser. No. 277*, 313 pp. (1951)

72. Gray, I., and Pulaski, E. J., *Proc. Soc. Exptl. Biol. Med.*, **78**, 421 (1951)

73. Gray, I., Siiteri, P. K., and Pulaski, E. J., *Proc. Soc. Exptl. Biol. Med.*, **77**, 626–27 (1951)

74. Greene, L. C., Stuart, E. G., and Joraleman, J., *Proc. Soc. Exptl. Biol. Med.*, **82**, 39–42 (1953)

75. Gropper, A. L., Cockrell, E. W., Raisz, L. G., and Pulaski, E. J., *Am. J. Physiol.*, **169**, 749–56 (1952)

76. Gropper, A. L., Raisz, L. G., and Amspacher, W. H., *Surg. Gynecol. Obstet.*, **95**, 521–42 (1952)

77. Grotte, G., Knutson, R. C., and Bollman, J. L., *J. Lab. Clin. Med.*, **38**, 577–582 (1951)

78. Halpern, B. N., Benacerraf, B., and Briot, M., *Brit. J. Pharmacol.*, **7**, 287–97 (1952)
79. Hammarsten, J. F., Heller, B. I., and Ebert, R. V., *J. Clin. Invest.*, **32**, 340–44 (1953)
80. Hampton, J. K., Friedman, J. J., and Mayerson, H. S., *Proc. Soc. Exptl. Biol. Med.*, **79**, 643–46 (1952)
81. Harkins, H. N., *Am. J. Physiol.*, **148**, 538–46 (1947)
81a. Harkins, H. N., *Ann. Rev. Med.*, **4**, 279–98 (1953)
82. Harroun, J. E., Smyth, C. J., and Levey, S., *J. Clin. Invest.*, **29**, 212–17 (1950)
83. Hartman, F. W., *Arch. Surg.*, **63**, 728–38 (1951)
84. Hartman, F. W., *Ann. N. Y. Acad. Sci.*, **55**, 504–10 (1952)
85. Hartman, F. W., and Behrman, V. G., *J. Am. Med. Assoc.*, **152**, 1116–20 (1953)
86. Haynes, B. W., Jr., Crawford, E. S., Mahaffey, J. H., and DeBakey, M. E., *Surg. Forum, Proc. 38th Congr. Am. Coll. Surg.*, 433–40 (1952)
87. Hehre, E. J., Sugg. J. Y., and Neill, J. M., *Ann. N. Y. Acad. Sci.*, **55**, 467–70 (1952)
88. Heidelberger, M., in Kabat, E. A., and Berg, D., *Ann. N. Y. Acad. Sci.*, **55**, 471–75 (1952)
89. Higgins, A. R., Harper, H. A., Kimmel, J. R., Burns, T. W., Jones, R. E., Smith, T. W. D., and Klein, C. L., *J. Appl. Physiol.*, **4**, 776–84 (1952)
90. Hoffmann, G. T., Rottino, A., and Albaum, H. G., *Science*, **144**, 188–89 (1951)
91. Jacob, S., Ravin, H., Frank, H. A., and Berry, D. W., *Proc. Soc. Exptl. Biol. Med.*, **78**, 784–87 (1951)
92. James, G. W., Purnell, O. J., and Evans, E. I., *J. Clin. Invest.*, **30**, 181–89 (1951)
93. James, G. W., Purnell, O. J., and Evans, E. I., *J. Clin. Invest.*, **30**, 191–99 (1951)
94. Kabat, E. A., and Berg, D., *Ann. N. Y. Acad. Sci.*, **55**, 471–75 (1952)
95. Kimura, K., Iijima, N., and Hara, R., *J. Pharm. Soc. Japan*, **72**, 1245–49 (1952)
96. Kimura, K., Iijima, N., and Hara, R., *J. Pharm. Soc. Japan*, **72**, 1249–52 (1952)
97. Kimura, K., Iijima, N., and Hara, R., *J. Pharm. Soc. Japan*, **72**, 1252–53 (1952)
98. Knisely, M. H., *Postgrad. Med.*, **10**, 15 (1951)
99. Koletsky, S., and Gustafson, G. E., *Proc. Soc. Exptl. Biol. Med.*, **75**, 776–78 (1950)
100. Kovach, A. G. B., and Takacs, L., *Nature*, **171**, 433–34 (1953)
101. Kovach, A. G. B., Takacs, L., Roheim, P., Kliss, S., and Kovach, E., *Acta Physiol. Acad. Sci. Hung.*, **3**, 345–55 (1952)
102. Kovach, A. G. B., Takacs, L., Menyhort, J., Iranyi, M., and Kalmar, Z., *Acta Physiol. Acad. Sci. Hung.*, **3**, 357–66 (1952)
103. Langohr, J. L., Rosenfeld, L., Owen, C. R., and Cope, O., *Arch. Surg.*, **59**, 1031–44 (1949)
104. Lafontaine, A., *Compt. rend. soc. biol.*, **144**, 430–32 (1950)
105. Lemley, J. M., and Meneely, G. R., *Am. J. Physiol.*, **169**, 61–65 (1952)
106. Levy, E. Z., North, W. C., and Wells, J. A., *Federation Proc.*, **12**, 342 (1953)
107. Loeffler, R. K., and Scudder, J., *Am. J. Clin., Pathol.*, **23**, 311–23 (1953)
108. Lusky, L. M., and Braun, H. A., *Antibiotics and Chemotherapy*, **1**, 58–59 (1952)
109. Lutz, B. R., *Physiol. Rev.*, **31**, 107–30 (1951)
110. McCarthy, M. D., *Ann. Surg.*, **136**, 546–51 (1952)
111. McCarthy, M. D. (Personal communication)
112. McCarthy, M. D., and Parkins, W. M., *Am. J. Physiol.*, **150**, 428–43 (1947)

113. McCarthy, M. D., and Draheim, J. W., *Proc. Soc. Exptl. Biol. Med.*, **79**, 346–49 (1952)
114. McCarthy, M. D., and Newlin, N., *J. Lab. Clin. Med.*, **41**, 416–20 (1953)
115. Marshall, L. A., Hanna, C. H., Specht, H., and Neal, P. A., *Proc. Soc. Exptl. Biol. Med.*, **79**, 363–66 (1952)
116. Mayer, R. A., and Ruben, J. E., *J. Phila. Gen. Hosp.*, **2**, 115–20 (1951)
117. Metcalf, W., and Rousselot, L. M., *Surg. Forum, Proc. 38th Congr. Am. Coll. Surgeons*, 428–33 (1952)
118. Michie, A. J., Koop, C. E., Blakemore, W. S., and Ragni, M. C., *J. Appl. Physiol.*, **5**, 621–624 (1953)
119. Michie, A. J., and Ragni, M. C., *J. Appl. Physiol.*, **5**, 625–627 (1953)
120. Miller, A. J., Shifrin, A., Kaplan, B. M., Gold, H., Billings, A., and Katz., L. N., *J. Am. Med. Assoc.*, **152**, 1198–1201 (1953)
121. Millican, R. C., and Rosenthal, S. M. (Unpublished data)
122. Millican, R. C., Stohlman, E. F., and Mowry, R. W., *Am. J. Physiol.*, **170**, 173–78 (1952)
123. Millican, R. C., Tabor, H., and Rosenthal, S. M., *Am. J. Physiol.*, **170**, 179–86 (1952)
124. Millican, R. C., Tabor, H., Stohlman, E. F., and Rosenthal, S. M., *Am. J. Physiol.*, **170**, 187–95 (1952)
125. Moore, D. H., *Am. J. Physiol.*, **173**, 131–37 (1953)
126. Moore, D. H., and Fox, C. L., Jr., *Nature*, **165**, 872 (1950)
127. Moore, D. H., Nickerson, J. L., Powell, A. E., and Marks, G., *Proc. Soc. Exptl. Biol. Med.* **77**, 706–9 (1951)
128. Moore, D. H., and Worf, D., *Am. J. Physiol.*, **170**, 616–23 (1952)
129. Moore, F. D., *Med. Clin. N. Amer.*, **36**, 1201–14 (1952)
130. Morrison, A. E., Lundy, J. S., and Essex, H. E., *Curculation*, **5**, 208–14 (1952)
131. Mowry, R. W., Longley, J. B., and Millican, R. C., *J. Lab. Clin. Med.*, **39**, 211–27 (1952)
132. Mowry, R. W., and Millican, R. C., *Am. J. Pathol.*, **29**, 523–45 (1953)
133. Mowry, R. W., and Millican, R. C. (Unpublished data)
134. Moyer, C. A., *Texas State J. Med.*, **45**, 635–39 (1949)
135. Moyer, C. A., in *Pub. Health Repts.* (*U. S.*), **65**, 1317–20 (1950)
136. Moyer, C. A., *Ann. Surg.*, **137**, 628–35 (1953)
137. Moyer, C. A., Coller, F. A., Iob, V., Vaughan, H. H., and Marty, D., *Ann. Surg.*, **120**, 367–76 (1944)
138. Moyson, F., and Gavosto, F., *Biochem. et Biophys. Acta.*, **10**, 479 (1953)
139. Mukherjee, S. R., *Brit. J. Urol.*, **24**, 52–54 (1952)
140. Munan, L. P., and Einheber, A., *Science*, **116**, 425–27 (1952)
141. Murphy, W. P., Jr., and Workman, W. G., *J. Am. Med. Assoc.*, **152**, 1421–23 (1953)
142. Narat, J. K., Casella, P. A., and Cangelosi, J. P., *Arch. Surg.*, **64**, 80–91 (1952)
143. Neal, W. B., Jr., Kark, A. E., Zubiran, J. M., and Montalbetti, J. A., *Arch. Surg.*, **65**, 774–82 (1952)
144. Nelson, A. A., and Lusky, L. M., *Proc. Soc. Exptl. Biol. Med.*, **76**, 765–67 (1951)
145. North, W. C., and Wells, J. A., *J. Pharmacol.*, *Exptl. Therap.*, **103**, 356 (1951)
146. Overman, R. R., *Physiol. Revs.*, **31**, 285–311 (1951)
147. Paine, R. S., and Janeway, C. A., *J. Am. Med. Assoc.*, **150**, 199–202 (1952)

148. Parkins, W. M., Perlmutt, J. H., and Vars, H. M., *Am. J. Physiol.*, **170**, 351–56 (1952)
149. Parkins, W. M., Perlmutt, J. H., and Vars, H. M., *Am. J. Physiol.*, **173**, 403–10 (1953)
150. Persson, B. M., *Acta Soc. Med. Upsaliensis*, **57**, 411–20 (1952); **57**, 421–37 (1952)
151. Plough, I. C., Teschan, P. E., and Seligson, D., *J. Lab. Clin. Med.*, **42**, 224–31 (1953)
152. Raisz, L. G., and Pulaski, E. J., *Am. J. Physiol.*, **169**, 475–82 (1952)
153. Randall, H. T., *Ann. N. Y. Acad. Sci.*, **55**, 412–28 (1952)
154. Ravich, R. A., and Revici, E., *Bull. Am. Soc. Hosp. Pharm.*, **8**, 23–26 (1951)
155. Reichman, S., You, S. S., and Sellers, E. A., *Can. Med. Assoc. J.*, **66**, 551–52 (1952)
156. Reinhardt, W. O., *Am. J. Physiol.*, **169**, 198–202 (1952)
157. Reinhold, J. G., von Frijtag Drabbe, C. A. J., Newton, M., and Thomas, J., *Arch. Surg.*, **65**, 706–13 (1952)
158. Reiss, E., Stirman, J. A., Artz, C. P., Davis, J. H., and Amspacher, W. H., *J. Am. Med. Assoc.*, **152**, 1309–13 (1953)
159. Rhinelander, F. W., Langohr, J. L., and Cope, O., *Arch. Surg.*, **59**, 1056–69 (1949)
159a. Rosen, H., and Levenson, S. M., *Proc. Soc. Exptl. Biol. Med.*, **83**, 91–97 (1953)
160. Rosenberg, E., Moore, C. R., Farmer, A. W., and Franks, W. R., *Nature*, **171**, 431–32 (1953)
161. Salzberg, A. M., and Evans, E. I., *Ann. Surg.*, **132**, 746–58 (1950)
162. Seeley, S. F., *Ann. N. Y. Acad. Sci.*, **55**, 446–50 (1952)
163. Seligman, A. M., Frank, H. A., and Fine, J., *J. Clin. Invest.*, **26**, 530–35 (1947)
164. *Shock and Circulatory Homeostasis Trans. 1st Conf.* (Josiah Macy, Jr. Foundation, New York, N. Y., 232 pp., 1952)
165. *Shock Syndrome* (New York Academy of Sciences, New York, N. Y., 1952); *Ann. N. Y. Acad. Sci.*, **55**, 345–542 (1952)
166. Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S., *Circulation*, **3**, 42–79 (1951)
167. Shorr, E., Baez, S., Metz., D. B., and Zweifach, B. W., *Federation Proc.*, **11**, 147 (1952)
168. Shrewsbury, M. M., Jr., and Reinhardt, W. O., *Am. J. Physiol.*, **168**, 366–74 (1952)
169. Skelton, J. A., Mills, L. C., and Moyer, J. H., *Federation Proc.*, **11**, 391 (1952)
170. Smith, D. L., and D'Amour, F. E., *J. Pharmacol. Exptl., Therap.*, **106**, 429–32 (1952)
171. Smythe, C. M., Maloney, J. V., Jr., Gilmore, J. P., and Handford, S. W., *Federation Proc.*, **12**, 135 (1953)
172. Steele, R., Van Slyke, D. D., and Plazin, J., *Ann. N. Y. Acad. Sci.*, **55**, 479–84 (1952)
173. Stohlman, E. F. (Unpublished data)
174. Stoner, H. B., Threlfall, C. J., and Green, H. N., *Brit. J. Pathol.*, **33**, 131–56 (1952)
175. Stopak, J., *Am. J. Physiol.*, **175**, 99–102 (1953)
176. Strawitz, J. G., Lee, W. C., Schmidt, E. R., and Orth, O. S., *Proc. Soc. Exptl. Biol. Med.*, **80**, 226–30 (1952)

177. Strumia, M. M., McGraw, J. J., and Sample, A. B., *J. Lab. Clin. Med.*, **40**, 211–22 (1952)
178. *Symposium on Burns* (National Research Council, Washington, D. C., 193 pp., (1951)
179. *Symposium on Shock* (Army Medical Service Graduate School, Washington, D. C., 1951)
180. Tabor, H., and Rosenthal, S. M., *Public Health Repts.* (*U. S.*), **60**, 371–81, 401–19 (1945)
181. Tabor, H., Rosenthal, S. M., and Millican, R. C., *Am. J. Physiol.*, **167**, 517–22 (1951)
182. Terkildsen, T. C., *Acta Physiol. Scand.*, **27**, 68–81 (1952)
183. Terry, R., and Yuile, C. L., *Federation Proc.*, **11**, 430 (1952)
184. Threlfall, C. J., Stoner, H. B., and Green, H. N., *Nature*, **168**, 279–98 (1951)
185. Turner, F. P., Butler, B. C., Smith, M. E., and Scudder, J., *Surg. Gynecol. Obstet.*, **88**, 661–75 (1949)
186. Veal, J. R., Russell, A. S., and Ashburn, F. S., *Ann. Surg.*, **136**, 485–94 (1952)
187. Wasserman, K., and Mayerson, H. S., *Am. J. Physiol.*, **165**, 15–26 (1951)
188. Wasserman, K., and Mayerson, H. S., *Am. J. Physiol.*, **170**, 1–10 (1952)
189. Wasserman, K., and Mayerson, H. S., *Am. J. Physiol.*, **171**, 218–32 (1952)
190. Westphal, V., DeArmond, R., Priest, S. G., and Stets, J. F., *J. Clin. Invest.*, **31**, 1064–68 (1952)
191. Westphal, V., Priest, S. G., and Stets, J. F., *Am. J. Physiol.*, **173**, 305–11 (1953)
192. Whitham, A. C., Fleming, J. W., and Bloom, W. L., *J. Clin. Invest.*, **30**, 897–902 (1951)
193. Wight, A., Raker, J. W., Merrington, W. R., and Cope, O., *Ann. Surg.*, **137**, 175–83 (1953)
194. Wilson, J. S., Estes, E. H., Jr., Doyle, J. T., Bloom, W. L., and Warren, J. V., *Am. J. Med. Sci.*, **223**, 364–69 (1952)
195. Winfield, J. M., Fox, C. L., Jr., and Mersheimer, W. L., *Ann. Surg.*, **134**, 626–34 (1951)
196. You, S. S., and Sellers, E. A., *Am. J. Physiol.*, **160**, 83–88 (1950)
197. Zanetti, M. E., *Am. J. Physiol.*, **171**, 538–44 (1952)
198. Zweifach, B. W., *Ann. N. Y. Acad. Sci.*, **55**, 370–80 (1952)
199. Zweifach, B. W., Baez, S., and Shorr, E., *Federation Proc.*, **11**, 177 (1952)

ANESTHESIA[1]

By Robert D. Dripps

*Department of Anesthesiology, Hospital of the University of Pennsylvania and the
University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

This review will have distinct personal overtones. Its primary aim is to
consider critically three controversial topics which are recent in their incep-
tion and possess potentialities of importance. Its secondary aim is to present
several recent developments of a more limited scope. In this way the review
may attract more widespread reader interest.

Curare Group

Little more than ten years ago curare was a medical curiosity. There were
no pure preparations. Injection of crude solutions into animals resulted in
such depression of blood pressure that the possibility of use in man seemed
remote. Pharmacology text books limited discussion of curare to a few para-
graphs in fine print. The development of the field was rapid, however, as soon
as a pharmaceutically acceptable product became available. d-Tubocurarine
was isolated in pure form. A variety of curariform drugs were then synthe-
sized. Intensive fundamental studies of nerve-muscle conduction were com-
pleted and a vast clinical experience was accumulated. Overenthusiasm
marked the reaction of many. Skepticism was equally apparent in other
quarters. Since the use of this type of drug is firmly established it seems per-
tinent to appraise the reasons underlying such varied opinions in an effort to
view the "curare-like" substances in their proper perspective.

The most important test which any therapeutic agent must pass is that
of safety. The basic difference in opinion revolves around the question of
"whether or not there is an increased mortality and morbidity rate following
the administration of curare drugs to man."

The most common use of curare substances is in surgical patients. The
compounds are administered primarily with the view of reducing the amount
of anesthetic agent required to produce satisfactory surgical working condi-
tions, i.e., muscular relaxation and blocking of untoward reflexes. Prior to
the introduction of the curare group profound muscular relaxation during
general anesthesia was achieved by relatively deep narcosis. This greater
degree of anesthesia is accompanied by greater danger to the patient during
operation and by a more disturbed postoperative course. One can therefore
turn to a study of anesthetized patients and rephrase the question stated
above to "whether the hazards of the curare drugs outweigh the disadvan-
tages of deeper general anesthesia."

It is the reviewer's opinion that this question has not yet been answered.
One approach to the problem would be to anesthetize alternate patients in

[1] The survey of literature pertaining to this review was completed in July, 1953.

comparable groups (age, sex, physical status, type, and severity of operation) with nitrous-oxide, oxygen, and ether on the one hand and nitrous-oxide, oxygen, and curare on the other.[2] In such a study, in addition to an analysis of death rate, careful records should be made of all three phases of anesthesia, induction, maintenance, and recovery. During induction, for example, the incidence of excitement, anoxia, laryngospasm, reduction of blood pressure and of pulse pressure might be listed. During maintenance one could record such data as the difficulties of pulmonary ventilation, problems associated with positive pressure inflation of the lungs, and the response of the circulation to surgical manipulations. During recovery one would be interested in the incidence of nausea, vomiting, headache, urinary retention, intestinal distention, time of ambulation, and adequacy of wound healing. A large series of patients with a variety of preoperative conditions must be included. In such a way, one might be able to determine the price paid by patients who did or did not receive curare drugs.

Although such a comprehensive study is not available, many potential dangers of the curare group are known and can be discussed in light of present knowledge. To appreciate the possibilities of harm it is necessary to understand the widespread pharmacological actions of the curare drugs. These are admirably described in Paton's recent review (1) where it is emphasized that, in addition to the production of nerve-muscle junction block, these compounds may block ganglionic transmission, cause the liberation of histamine, and stimulate or depress synapses in the central nervous system. Thus, drugs which at first glance appear to have a localized and limited site of action, namely at the nerve-muscle junction, in reality exert effects on many other tissues. The protean nature of the body's response to a curare drug must be recalled as one attempts an analysis of the undesirable reactions which have been described.

Abnormal respiratory responses.—All of the curare drugs, when injected into man, can reduce the minute volume of respiration or produce apnea. It is usually assumed that this respiratory effect is the result of block at the neuro-myal junction of the muscles concerned with breathing. As a corollary of this, it is believed that as soon as the nerve-muscle junction blockade begins to decline, respiration will return towards normal. Recent data suggest that such explanations are imcomplete (2).

A study of 2800 patients receiving a curare drug during anesthesia has been reported (3). At the completion of the surgical procedure, six patients were in apnea from 50 to 140 min. after conclusion of the operation. Seven others required assistance to respiration from 70 to 130 min. postoperatively. In other words, 0.46 per cent of this series exhibited untoward respiratory re-

[2] The latter method is rarely used in clinical practical. Thiopental (Pentothal) is usually added for greater flexibility. This introduces a variable which has not been evaluated by those discussing the dangers of the curare drugs. Thiopental carries with it certain dangers, and sequelae blamed upon the curare group are often caused by thiopental.

sponses. No control data were presented but the statement was made that apnea at the end of operation had never been observed without the previous injection of a curare drug. There was no apparent relationship between the respiratory effects and the age or sex of the patient, or the anesthetic agents administered. Apnea occurred significantly more often in the patients whose preoperative physical condition was below normal. The curare drug selected appeared unimportant except where d-tubocurarine was injected after the administration of decamethonium bromide (Syncurine). Similar studies in a series of 698 patients receiving decamethonium bromide, Mytolon, or Flaxedil[3] indicated that at the end of anesthesia respiratory activity was satisfactory in only 75 to 88 per cent of the subjects (4). It is evident that at least some of the curare agents may act for an undesirably prolonged period of time.

Theoretically, decreased respiratory minute volume or apnea could result from depression of the respiratory centers in the brain or from more peripheral involvement of nerves and muscles concerned with breathing, e.g., depression or abolition of nerve conduction, conduction through the neuromyal junction, or of muscular contraction itself. There is evidence that both peripheral and central mechanisms may be involved in the unusual respiratory responses to curare drugs.

It has been demonstrated in man and animals that apnea can persist after apparent restoration of neuro-muscular transmission. There are reports (3, 6) of patients able to move their extremities, open their eyes and swallow, yet who remain apneic after administration of various curare compounds. Electrical stimulation of the phrenic nerve can be shown to cause contraction of the diaphragm under these conditions, indicating that nerve-muscle transmission is possible at least artificially. Similarly electrical stimulation of thoracic anterior spinal roots is followed by contraction of intercostal muscles (7). Finally, the intravenous administration of alpha-lobeline may be followed by restoration of spontaneous respiratory activity in animals made apneic with curare drugs (2). Presumably alpha-lobeline acts via the respiratory center, not at the nerve-muscle junction. These data do not reveal the basic abnormality involved in prolonged respiratory depression but they strongly suggest a central component. There might be direct depression of brain cells concerned with respiration. Concomitant anoxia or hypercarbia might exaggerate such an effect; or spontaneous respiration may depend upon the integration of centripetal impulses susceptible to the curare compounds. Hunt & Kuffler (8) offer one possibility, a blocking action of curare drugs on proprioceptive spindle mechanisms. The conclusion seems inescapable that in some patients respiratory depression need not be caused by block of nerve-muscle conduction, but by a more central disturbance.

Other data draw attention to the possible role of prolonged neuromuscular block in the production of abnormal respiratory responses to cu-

[3] [v-phenenyltris (oxyethylene)] -tris [triethylammonium iodide].

rare. Potassium deficiency, not uncommon in surgical patients, may be associated with increased susceptibility at the nerve-muscle junction to the blocking action of curare (9). The antagonism between potassium and *d*-tubocurarine has been demonstrated (10). Abnormalities of metabolism of other electrolytes concerned with nerve-muscle transmission such as calcium or magnesium may also be a factor, although relevant data are not at hand.

A final aspect in the problem of abnormally prolonged and profound curare action is the fate of these drugs in the body. Marsh (11), in a well conceived and well executed series of experiments, has studied the distribution and rate of destruction and elimination of certain curare drugs in man and animals. His data indicate that metabolism and excretion of these products is slow, and that the relatively brief paralytic action normally noted is attributable to rapid redistribution of the intravenously injected drugs. With larger doses which saturate indifferent depots, the paralytic effects tend to be more prolonged and become dependent upon the rate of metabolism and excretion. Since extra-vascular compartments can hold about half a given dose of *d*-tubocurarine, a considerable amount of material can be stored temporarily following two or three injections within less than an hour. If there is later dehydration or electrolyte or fluid shift, sufficient *d*-tubocurarine may be mobilized back into the plasma to bring about further paralysis or delayed reparalysis.

Histamine liberation.—Many bases used in medicine (such as morphine, meperidine, atropine, the trypanocidal diamidines) can release into the circulation the histamine which is normally held by the tissues in some unknown but inactive form. *d*-Tubocurarine appears to liberate histamine more readily than any of the other drugs in the curare group. Such a release may be associated with any of the known actions of histamine, including bronchoconstriction, hypotension, increase in gastric acidity, and change in capillary permeability. According to Landmesser, Converse & Harmel (5), bronchoconstriction following the intravenous administration of *d*-tubocurarine can be measured in man. Apparently this response occurs much less regularly in the anesthetized patient than in the laboratory animal. The depressant effect of anesthetic agents upon the action of histamine may afford a partial explanation for this. The possibility of histamine liberation and action must be considered, particularly during lighter planes of anesthesia and when *d*-tubocurarine is the drug selected.

Circulatory effects.—As one reconstructs the events leading up to the deaths following use of the curare drugs, it is evident that in addition to the respiratory abnormalities already discussed (depression, apnea, bronchoconstriction) circulatory inadequacy is frequently evident. The role played by the ganglionic blocking action of the curare drugs in such circulatory depression is difficult to assess, but must be considered. With any degree of blockade one can anticipate interference with vasomotor reactivity and compensation. Another important cause for circulatory depression is the positive pressure inflation of the lungs required during the respiratory depressant

action of curare compounds. Reduction of arterial pressure in response to raised airway pressure has long been recognized. As already pointed out, many clinicians combine thiopental with curare drugs. Thiopental *per se* has been shown to cause tachycardia and decreased arterial mean pressure and pulse pressure (12). Of even greater interest was the observation that positive pressure inflation of the lungs produced significantly greater arterial hypotension in patients anesthetized with thiopental than in the same subjects during consciousness. The implication of this to patients receiving curare and thiopental is evident. Should histamine be liberated and should hypoxia and hypercarbia supervene, additional stresses might be expected on the circulation.

The majority of the studies referred to above have been carried out on *d*-tubocurarine, Flaxedil, decamethonium bromide, Mytolon, and Metubine. As the defects in these various compounds become better known, search for less toxic and more controllable curare products was stimulated. This has resulted in the clinical evaluation of succinylcholine, a compound first synthesized in 1911.

Succinylcholine.—Succinylcholine (Anectine, Scoline) is di-acetylcholine, i.e., two molecules of acetylcholine joined together at one end. The duration of action after a single intravenous injection is brief, ranging from two to five minutes. The brevity of effect appears related to the fate of the drug in the body, i.e., its destruction by serum pseudo-cholinesterase. Brief periods of relaxation can thus be provided by single injections of 20 to 40 mg. for such procedures as endoscopy, reduction of fractures, and electroshock therapy.

If more prolonged relaxation is required the drug may be administered, as a continuous intravenous drip, in doses of 2 to 8 mg. per min. Regulation of the rate of flow affords relaxation of any degree. Cessation of flow is usually followed by a prompt return of normal muscle tone. Thus, for the first time, relative control of effect seems possible (13). Two theoretical objections to continuous infusion have been raised by Paton (1). First, it is possible that products of hydrolysis may be active. With single injections, only negligible quantities of succinylmonocholine or choline will be released; but with prolonged infusion, large amounts will accumulate. Second, side effects not seen with the smaller doses may be produced. These would include stimulation of vasomotor ganglia by the products of hydrolysis, resulting in a rise in blood pressure. Large doses of succinylcholine can also release histamine. On the basis of available clinical reports these hazards are not common (14, 15, 16, 17). At least a dozen instances of prolonged respiratory depression have been recorded, however, and the thesis of "controllability" with succinylcholine must be regarded as of relative proportions.

Succinylcholine, like decamethonium bromide, produces nerve-muscle block by depolarization. The question has been raised whether a persistent end-plate depolarization is dangerous. Paton (1) believes this unlikely. As he points out, a far more extensive depolarization of the whole length of the muscle fibers of the body takes place during vigorous muscular exercise. It

seems that neither overstimulation nor understimulation of the end-plate damages it, provided that the organism as a whole is protected from asphyxia.

Summary.—The reviewer's attitude toward the curare group of drugs can be summarized as follows. The balance sheet is in favor of these substances. In the United States the doses used are more conservative than abroad, where it is frequent to double or triple the amounts administered here. With this more cautious approach, it is the reviewer's belief that these drugs carry little if any hazard to the patient whose preoperative physical condition is within normal limits. Indeed, the sparing of deeper planes of anesthesia for such patients may well result in smoother, safer convalescence. There are data to suggest that the incidence of untoward reactions to the curare group rises as the physical condition of the patient deteriorates. Further knowledge of the basic pharmacologic action of these substances is needed so that those situations in which susceptibility may occur can be better defined. It must be recognized also that all types of anesthesia are more hazardous in the patient with dehydration, electrolyte imbalance, and such complicating factors as heart, kidney, renal or pulmonary disease. Comparative statistics are not yet available to indicate whether use of the curare drugs in such patients is attended by more problems than would more intense narcosis. This would appear to be a distinct possibility.

Several practical factors may have contributed to the early doubts of some. It is unfortunate that *d*-tubocurarine was the first drug introduced. Use of this substance, in the reviewer's experience, is more often accompanied by hypotension; there is a greater tendency for the liberation of histamine and the duration of action is prolonged. Had one of the newer muscle relaxants been the drug from which the majority of anesthetists gained their initial experience, the early results might have been more favorable. Overdosage was not infrequent in the opening years of the "curare decade" just past. We have now become more familiar with the possibilities of harm and also more balanced in our thinking.

CONTROLLED OR DELIBERATE HYPOTENSION

The deliberate reduction of arterial blood pressure in an effort to produce a relatively bloodless field for operation is being re-explored by a number of workers using new techniques (18 to 24). This is a challenging concept and one worthy of careful study, since its successful application might minimize the need for blood transfusions, reduce the incidence of transfusion reactions, reduce the cost of medical care, improve the results of certain operative procedures by minimizing bleeding, decrease operating time, and at the same time provide further insight into vascular readjustments during hypotension.

For many years neurosurgeons have recognized the value of low blood pressure in reducing or controlling bleeding. As an outgrowth of this, Gardner and Hale (1945) developed a technique of arterial bleeding which they have used during operations. Other methods of producing a lowering

of blood pressure involve use of spinal or epidural anesthesia, the intravenous administration of autonomic ganglionic blocking agents such as the penta-methonium or hexamethonium salts, or the application of positive pressure to the airway. After these measures have been instituted, further hypoten-sion may be achieved by the head-up position and/or by positive pressure controlled or assisted respiration.

Before considering the safety of deliberate hypotension, it may be worth emphasizing the desirability of reducing the number of whole blood trans-fusions administered to surgical patients. The incidence of post transfusion viral hepatitis continues to be a hazard (25). Sensitization of a recipient to subsequent transfusions has always posed a problem. With the discovery of numerous Rh subgroups an important source of sensitization was uncovered. Other similar but as yet incompletely studied factors remain to be evaluated (26). The cost of transfusions to the patient, the availability of whole blood, and the proper temperature for storing blood are problems requiring solution. The occurrence of generalized, unmanageable bleeding from traumatized surfaces during operation appears related to multiple blood transfusions in certain instances (27). Blood stored for more than a few days suffers almost a total loss of platelets, a reduction in the amount of accelerator globulin, one of the substances which acts as a catalyst in the formation of thrombin from prothrombin, and an increase in potassium. Furthermore, with passage of time increasing fragility of stored cells occurs so that approximately 30 per cent of the infused red cells may be destroyed within 24 hr. if a trans-fusion consists of blood more than 14 days old. For these various reasons one would like to decrease the number of transfusions.

The improvement in surgical working conditions attributed to the lowered blood pressure also deserves analysis. There can be no question but that capillary oozing can prolong an operation if not actually prevent its successful conclusion. Bleeding from larger vessels can be severe during de-liberate hypotension, however, and unless this blood is replaced as it is lost the result may be catastrophic. Data are needed comparing the extent of blood loss during operation of comparable extent and in comparable groups of patients. Proof of the sparing action of deliberate hypotension on blood loss is sketchy at the moment. Likewise, there is little convincing evidence of the decreased operating time and more adequate type of surgery which has been attributed to the lowered arterial pressure. Postoperative hemor-rhage, although not reported frequently, is always a possibility as the pres-sure-head returns towards normal following operation. There is danger lest this procedure be attempted in instances in which perfectly satisfactory re-sults can be obtained otherwise.

The patient during hypotension.—Every anesthesiologist has seen patients with acute reduction of arterial pressure during spinal anesthesia who have had warm, dry skin, good color, a full peripheral pulse, and a reasonable pulse pressure. If the patient were conscious, an alert state of mind and the absence of restlessness or anxiety, air hunger, chest or arm pain, taken to-

gether imply that there existed adequate cerebral and coronary arterial blood flow. These functions are more difficult to evaluate in the unconscious patient. Thus, one can readily admit to having observed patients whose level of blood pressure has been as low as 70 mm. Hg systolic but who have appeared to be otherwise in good condition. One must also admit, however, that other patients with similar levels of blood pressure have developed ischemic lesions of the brain, heart, or kidneys, and possibly liver (28) attributable to either an inadequate flow of blood through patent vessels, or to an actual occlusion of vessels by thrombosis or vasospasm. It is difficult to prove that blood pressure causes these complications, but the burden of proof is on those who deny the likelihood of relationship between the two.

Of the factors which determine whether the body can tolerate hypotension, the following would appear to be of significance:

(a) The duration of the hypotension.

(b) The degree of the hypotension.

(c) The previous condition of blood vessels; particularly those supplying the heart, brain, kidneys, and liver. If these vessels are sclerotic or otherwise abnormal, changes in their caliber in response to hypotension may not occur as readily as with normal vessels and an insufficiency of blood flow may result.

(d) The metabolic needs of the tissues during hypotension, again with particular emphasis on the heart and brain. The lower the metabolic requirements, the greater is the reduction in the supply of blood which can be tolerated. Thus, the general cellular depression as associated with general anesthesia may be a relative safeguard during periods of low blood pressure, since the tissue requirements are presumably lowered at the same time. Likewise, the heart may be better protected than one might imagine, because it is being called on to do less work if there be lessened peripheral arterial resistance. The coronary arterial blood supply may be curtailed but so may the demand for this blood.

(e) The liberation of specific depressant substances from ischemic tissues. Schoor's demonstration that a vasodepressor material for mesenteric blood vessels may be formed in the livers of shocked animals has possible widespread implications. This may only be the first of a group of toxic products so formed, the impact of which on the body as a whole may be serious.

The successful use of deliberately produced arterial hypotension will depend on whether nutrition for the heart, brain, and liver can be maintained during the period of low blood pressure. The kidney apparently will survive reasonable insults. Therefore, the clinician electing to employ this procedure must be able to predict which patient will tolerate it. Most observers will agree that young, healthy subjects can withstand reduced blood pressure satisfactorily. Most will agree that aged subjects with sclerotic vessels and previous histories of coronary, cerebral, or renal insufficiency are poor candidates. Who, today, can select the safe point between these two extremes?

Arfonad.—The most recent method for the deliberate production of

hypotension during anesthesia is the continuous intravenous injection of Arfonad (29 to 31). This drug, first introduced for the treatment of acute pulmonary edema (32) and toxemia of pregnancy (33), is a thiophanium compound with a brief duration of action. The situation is somewhat analogous to the use of succinylcholine in that because of the brevity of effect of each of these powerful substances, both are administered as a constant intravenous infusion. Control of action is regulated by the rate of flow. As with succinylcholine, cessation of flow is usually followed by a return of normal function within a few minutes. The lowering of blood pressure by Arfonad is thus more controllable than with the hexamethonium salts, deliberate arterial bleeding, or spinal anesthesia.

Arfonad apparently exerts its hypotensive effect through several mechanisms, primarily peripheral vasodilation and ganglionic blockade (34, 35). Liberation of histamine has also been suggested. The most interesting facet of its action, i.e., its brevity, is not yet explained, for the fate of this compound in the body is unknown. Considerable individual variation is demonstrated in the dosage response. Some patients respond to 0.5 to 1.0 mg. per min. while others require as much as 30 times this amount. The hypotension can usually be promptly reversed by the intravenous administration of a sympathomimetic amine.

Observations of patients receiving Arfonad have led to some interesting tentative conclusions. It is believed that once hypotension has been established, the need for general anesthesia is reduced considerably. This clinical impression is a reasonable one for the status of the patient is somewhat that of hibernation. It deserves investigation by quantitative methods. Body temperature is alleged to decline with rectal temperature reaching 97° F. Surgical shock is reported to be less frequent following such deliberate hypotension. If this can be proven, it will constitute a valuable bit of information to add to the data of those who believe that "shock" can be minimized or even treated by adrenergic blocking agents.

A sufficient clinical experience with Arfonad has not yet been reported to permit evaluation of the safety of the procedure. In one small series, a patient with previous hepatic disease suffered additional liver damage. In other series, tachycardia (up to 160 per min.) proved disturbing. The technique would seem to provide greater control, but the hazards of hypotension previously listed remain to some degree.

NEUROLOGICAL COMPLICATIONS OF SPINAL ANESTHESIA

In 1944 and again in 1950, Foster Kennedy wrote on the neurological complications of spinal anesthesia (36, 37). In the latter report, 12 cases of grave paralyses following the use of this method of anesthesia were reviewed. The last two paragraphs in this article are as follows: "From a neurological point of view we give the opinion that spinal anesthesia should be rigidly reserved for those patients unable to accept a local or general anesthetic. Paralysis below the waist is too large a price for a patient to pay in order that

the surgeon should have a fine relaxed field of operation." These forthright statements received widespread publicity in the press and in lay periodicals. Patients facing operation who are familiar with Kennedy's opinion are naturally alarmed if spinal anesthesia is selected for them. Physicians are confused and uncertain as to the status of this method. Although a definite answer cannot be given at this time on the basis of available data it would be amiss for the author of this review not to comment upon Kennedy's observations since they constitute one of the most challenging developments in anesthesia during the past few years.

That unfortunate sequelae may occur following spinal anesthesia cannot be denied. Before a sweeping indictment of the method is made, however, many points deserve consideration. The incidence of neurological complications following spinal anesthesia is unknown. The 12 instances recorded by Kennedy's group may represent an incidence which, if substantiated, would indicate that spinal anesthesia was more dangerous than general anesthesia. They may, however, have come from a large population. Some of the 12 patients were individuals with pre-existing nervous system disease in whom selection of the technique was unwise (38). In some, faulty technique may have contributed to the damage.

What data are there to justify the continued employment of spinal anesthesia? During the past five years the reviewer and his associates have attempted to follow every patient to whom spinal anesthesia had been given, not only while the individual was in the hospital but also for 6 to 48 months after operation. To date, 88 per cent of approximately 9000 patients have been followed in this fashion (39). The significance of such a detailed follow up is apparent. The literature contains many reports which exonerate spinal anesthesia, yet the data on which such conclusions are based have been gathered by a cursory follow up, inspection of routine hospital charts, or with no attempt to follow patients after discharge. Such analyses are limited in scope and cannot be expected to provide answers to the basic problem. So much is missed by the "ordinary" type of follow up. For example, limitation of visits to the first few postoperative days will often fail to uncover typical postlumbar puncture headache. Many of these commence after the patient has left the hospital. This is particularly true of young people discharged promptly after an apparently uneventful surgical convalescence. Diplopia frequently is first noticed on the eighth to tenth postoperative days and may not be recorded if the follow up ceases prior to that time. Finally, Kennedy has pointed out, such tragic meningeal reactions as adhesive arachnoiditis may first cause major symptoms weeks after the anesthesia.

On the basis of this long-term study, the reviewer divides the sequelae of spinal anesthesia into those incident to the mechanical damage of lumbar puncture and those secondary to the action of the anesthetic or other chemical agents (40). In the first group can be included most instances of headache, backache, diplopia, difficulties in hearing, injury to intervertebral discs, injury to nerve tissues secondary to direct trauma, and some instances of localized

or generalized infection such as infected intervertebral disk, extradural abscess, or meningitis. Refinements of the technique of lumbar puncture will reduce the incidence of sequelae significantly. Detailed attention to the following is essential (41).

(a) Sterilization of spinal anesthesia equipment and drugs; (Autoclaving is best). An indicator which responds to heat should be on each tray to prevent use of trays which have not been autoclaved. Epinephrine is the only substance injected into the subarachnoid space which has not been autoclaved. It should be immersed in a deeply colored solution so that an ampule crack can be recognized because of discoloration of the solution.

(b) Handling of syringes and needles by the anesthetist; if one is careless, powder or the skin antiseptic may contaminate the lumbar puncture needle or the syringe which is to contain the spinal anesthetic solution. Powder must be wiped off the anesthetist's gloves before any manipulations are begun. The skin antiseptic must not be spilled on the tray or allowed on the gloves.

(c) Performance of lumbar puncture; a number of structures must be pierced before the subarachnoid space can be reached with a needle. If a sharp, small-gauge needle is expertly introduced, trauma will be minimal. If a dull, large-bore needle is used, or if multiple explorations of the back are required, the extent and degree of injury are increased. The tissues which must be punctured are the spinal ligaments and meninges. Those which may suffer in addition are the periosteum, annulus fibrosis of the intervertebral disk, perivertebral plexus of veins, spinal cord, nerve roots, and blood vessels which accompany the latter in the subarachnoid space. Significant sequelae may follow injury to any of these structures (40).

Backache may be caused by injuries to the spinal ligaments, periosteum, or annulus fibrosis. Experimental as well as clinical data exist to support this contention. If hypertonic saline solution is injected into muscles, ligaments, or periosteum in the lumbar region, a deep aching pain results. When radiation of this pain occurs, it is to the low back. The pain is characteristic and reproducible. Presumably, injury to these deep structures by the lumbar puncture needle could reproduce conditions of the experiment, and lumbosacral pain might result.

The needle may pass beyond the subarachnoid space and damage the annulus fibrosis. The disk must be regarded as pain sensitive. Histological evidence of sensory innervation indicates that it is in all probability the ligamentous covering of the disk which is responsible for the pain. Irritation of or pressure against this covering might therefore cause low back pain. More extensive damage to the annulus fibrosis may be followed by herniation of the disk, a sequel of lumbar puncture reported by a number of workers. We have seen gelatinous material drip from a needle which entered the nucleus pulposus of a 14-year-old girl who inadvertently moved as the needle was being advanced during lumbar puncture.

Blood vessels may be perforated during lumbar puncture. Those of most

concern are the perivertebral plexus of veins and vessels which accompany nerve roots. Injury to the former is a common cause of a "bloody tap." Bleeding so produced may result in formation of an epidural hematoma, or if the blood gains access to the subarachnoid space, in signs of meningeal irritation. Damage to the vessels accompanying nerve roots may produce ischemia of these structures with possible subsequent neurologic signs and symptoms.

Nerve roots or rarely the spinal cord itself may be injured by the needle. Observation of 129 adult cadavers by Reimann and Anson in 1944 indicated that in 94 per cent of specimens the spinal cord ended in the region of the first or second lumbar vertebral bodies. In some instances however, the cord terminated as low as the middle of the third lumbar vertebral body. It is obvious that lumbar puncture should be performed with great caution above the interspace between L3–4. This is particularly true in infants or young children in whom the cord length more closely approximates that of the spinal canal.

Contact with the sensory roots of the cauda equina occurred in 13 per cent of the lumbar punctures performed by us for spinal anesthesia. Evidence of such contact was the development of "electric shocks" or pain sensations radiating into the back, perineum, or legs. Contact with motor roots might not be as evident to the operator unless muscular contractions resulted. Obviously, neurological sequelae do not occur with this frequency, but prolonged and occasionally permanent sensory or motor abnormalities may result from such direct trauma.

The second group of complications of spinal anesthesia is related to the introduction of a chemical agent into the subarachnoid space. This agent may, if the technique is faulty, be a skin antiseptic or detergent (42). In any event there must be a local anesthetic injected. The use of local anesthesia is predicated on the belief that its action is reversible. In the absence of pre-existing neurologic damage this is true in the majority of instances. Because of some abnormality, unrecognized or latent, the resistance of nerve tissue may be decreased, and a local anesthetic agent may cause interruption of function either for a long period or permanently. As Wilson, Rupp & Wilson (53) have emphasized, "An adequate neurologic history and examination should be complete for every patient considered for spinal anesthesia." Another anesthetic method should be chosen if a history of previous neurologic disorder is elicited or if any abnormalities are observed.

Even in the absence of pre-existing disease of the nervous system the reviewer believes that spinal anesthesia may cause diffuse irritation of nerve roots or cord substance. The more one searches for it, the more one can find a syndrome characterized by shooting pains in the legs, aching or soreness in the thigh muscles, or what is described by patients as a "drawing sensation in the legs." This may be noticed during the operative day, for a day or two after operation, may continue for a week, or may persist for months. The majority of these individuals show little in the way of objective neurologic

changes. One of our consultants described such patients as showing a "picture of irritation with a minimum of neurologic deficit." The incidence of this syndrome was 0.8 per cent in our series. This includes even very mild reactions. The majority of this group (65 per cent) had only transient complaints, i.e., less than 7 to 10 days. Admittedly, a functional component may exist in some of these patients' complaints. Old age, disorders in blood supply, the assumption of unusual positions during operation, e.g., lithotomy and Sims, may also have played a role. We are convinced nonetheless that, although the incidence of reactions is low, the meninges and nerve tissue in the subarachnoid space resent interference. Following lumbar puncture alone, there is an outpouring of cells and an alteration in proteins. This response may be exaggerated after the addition of a local anesthetic. Until more is known of the factors underlying such a reaction it can only be regarded as one of irritation. This meningeal response, usually aseptic, may only result in signs of nerve root or conus irritation. On the other hand, its final result may be the laying down of adhesions which may possibly choke off the blood supply to nerve elements and cause permanent disability.

It is to this latter reaction that Kennedy and his associates have given the descriptive name chronic progressive adhesive arachnoiditis. It is this complication to which they again refer in their latest article. It is a disabling, crippling, if not fatal, syndrome and it can follow spinal anestheisia. In 9000 cases we have not seen a single instance of such a reaction despite an 88 per cent follow up for more than six months. A year before our study was inaugurated, however, we did find one such patient. This puts our incidence at 1 in 12,000 for the past six year period. Obviously this may not be the absolute figure for such a complication. It is not logical to condemn so useful a method until the incidence of the serious complications has been clearly defined by long-term studies. Our study suggests that spinal anesthesia is safe and reliable if certain precautions are taken.

Several articles have recently appeared in defense of spinal anesthesia (43 to 45). These support the position taken by the reviewer. Reports of unfortunate sequelae have also continued to occur (38, 42, 46). It is believed that the explanations advanced in this text for such complications are valid.

Opiate Antagonism

A recent development of interest has been the apparent ability of nalorphine (*N*-allylnormorphine; Nalline) to counteract the respiratory and circulatory depressant action of the opiates in man (47 to 51). This drug, which is a close relative of morphine from the standpoint of chemical structure, is effective in patients who are suffering from overdosage of morphine, dihydromorphinone (Dilaudid), methadon, metopon, meperidine (Demerol), Pantopon, Dromoran and prisilidene (Nisentil). The drug is not effective against barbituric acid derivatives, inhalation anesthetic agents, or other nonopiate central nervous system depressants studied (48). It is injected

intravenously in doses ranging from 5 to 15 mg. Its most striking effect, noted within the first minute of injection, is respiratory stimulation. Both the rate and minute volume of breathing are restored toward normal. According to published data a respiratory rate as low as 1 to 2 per min. because of opiate overdosage may be promptly increased to 14 to 16 per minute (47). If circulatory depression, i.e., low blood pressure, is part of the clinical picture of opiate poisoning, nalorphine has proven cabable of exerting a pressor effect. The drug does not possess a marked analeptic or awakening action. In some patients an elevation in the level of consciousness is observed, but in others, despite the obvious improvement in respiration and circulation the patient's sensorium remains clouded. Nevertheless, the drug represents a definite advance in the therapy of accidental or deliberate opiate overdosage.

Nalorphine has been used in an effort to reduce the incidence of asphyxia neonatorum. Any benefits noted would in all probability be related to antagonism of opiates used in the mother for analgesia during labor. The drug is injected intravenously into the mother approximately ten minutes prior to the anticipated time of delivery. Since the opiates are transferred across the placenta and enter the fetal circulation, nalorphine has also been injected directly into newborns who appear depressed from predelivery narcotics (48). A dose of 0.2 mg. is injected into the umbilical cord vein for this latter purpose.

There has been a tendency on the part of some obstetricians to increase predelivery doses of opiates, relying on the reversal action of nalorphine to prevent excessive depression. This must be regarded as a hazardous practice until data are available to indicate otherwise.

Another interesting field of usefulness for nalorphine is in the detection of opiate addiction (52). Administration of 5 mg. nalorphine to individuals addicted to morphine or methadon induces abstinence symptoms within 15 min. These reach a maximum intensity in 30 min. and persist for 2 to 3 hr. A larger dose (30 mg.) of the substance may cause severe abstinence effects with marked delirium. A similar though perhaps less dramatic response is observed in meperidine addicts. If these observations are confirmed, nalorphine may be a useful tool in diagnosing and assessing the degree of physical dependence in individuals suspected of addiction. It would no longer be necessary to isolate such persons and observe them for periods of 36 hr. or longer. If they have a true physical dependence, the fact could be ascertained within 15 min. by injecting a small dose of nalorphine.

One cannot help speculate about the chemical structure of nalorphine. It is structurally identical with morphine except for the replacement of a methyl group, yet it is effective against meperidine (Demerol), the formula for which is quite different. Finally, if nalorphine is injected into normal man, it produces respiratory and circulatory depression (47). One thus has a drug which is depressant when used alone, but is stimulant when administered to

patients who have received opiates. This chemical deserves considerable study.

Transtracheal Topical Anesthesia

The pharynx and larynx are usually anesthetized for endoscopy by spraying these regions through the nose or mouth, or by applying pledglets of cotton soaked in the anesthetic solution. The transtracheal route involves injection of the local anesthetic drug in the trachea via a 23-gauge needle placed through the crico-thyroid membrane (54). One or two cc. of a 5 to 10 per cent cocaine, 2 per cent tetracaine or 2 per cent lidocaine (Xylocaine) solution are rapidly introduced. The resulting cough distributes the anesthetic agent over the vocal cords and oropharynx. The patient is awake and is instructed not to cough, swallow, or talk while the needle is in place. The technique was first described 50 years ago, but has recently been reintroduced.

Proponents of the method point to the speed with which this maneuver can be completed, since an oral spray required anesthetization of the tongue and pharnyx before the nebulizer can be advanced toward the vocal cords. It is also claimed that patients prefer this route to the oral.

Before this procedure can be endorsed, however, a critical appraisal of sequelae should be made. One can think of a number of possible hazards including: (a) breaking of the needle; (b) sudden absorption of the volatilized drug into the pulmonary circulation with resulting reflex or direct depression of blood presure; (c) development of mediastinal emphysema; (d) localized infection spreading to involve the mediastinum; and (e) hemorrhage.

It seems doubtful that the advantages of the technique warrant the risks involved, but perhaps this is too conservative an attitude.

Trichlorethylene

Trichlorethylene (Trilene, Trimar) has never been a popular inhalation anesthetic agent in the United States. During the London "Blitz" British anesthetists, searching for nonexplosive drugs, began to re-explore the utility of trichlorethylene (55). Starting in England and spreading to Canada, interest in this substance finally prompted Americans to try it clinically. During the last few years data have been reported which suggest that the volatile liquid may have certain uses, chiefly for obstetrics, outpatient anesthesia, and in operations which do not require muscular relaxation or profound depth of anesthesia (56, 57).

The drug has several unusual properties. If administered in too high a concentration, it causes an increase in respiratory rate not infrequently reaching 50 to 60 per min. It is apparently a powerful analgesic, whether more so than divinyl or ethyl ether remains to be proven, although clinical opinion suggests this. Nausea and vomiting are alleged to be uncommon fol-

lowing its administration. Induction is not unpleasant and awakening is usually prompt.

Because of its low volatility, open drop administration is difficult and the drug is therefore given by means of a specially constructed inhaler, or via a standard anesthesia machine. Volatilization with a mixture of nitrous-oxide and oxygen is currently popular. A closed system cannot be used since the drug reacts with soda lime to form dichloracetylene. Cardiac arrhythmias are not infrequent.

If the analgesic properties of trichlorethylene can be substantiated this substance may find a niche, although it is difficult to believe that it will be a drug of great usefulness.

LITERATURE CITED

1. Paton, W. D. M., *Anaesthesia*, **8**, 151–74 (1953)
2. Ellis, C. H., Morgan, W. V., and deBeer, E. J., *J. Pharmacol. Exptl. Therap.*, **106**, 353–63 (1952)
3. Dripps, R. D., *Ann. Surg.*, **137**, 145–55 (1953)
4. Foldes, F. F., Machaj, T. S., Hunt, R. D., McNall, P. G., and Carberry, P. C., *J. Am. Med. Assoc.*, **150**, 1559–66 (1952)
5. Landmesser, C. M., Converse, J. G., and Harmel, M. H., *Anesthesiology*, **13**, 275–80 (1952)
6. Little, D. M., Jr., Hampton, L. J., and Grosskreutz, D. C., *Current Researches Anesthesia & Analgesia*, **32**, 171–80 (1953)
7. Console, A. D., *Ann. N. Y. Acad. Sci.*, **54**, 491 (1951)
8. Hunt, C. C., and Kuffler, S. W., *J. Pharmacol. Exptl. Therap.*, **98**, 96–107 (1950)
9. Foldes, F. F., Hunt, R. D., and Ceravolo, A. J., *Current Researches Anesthesia & Analgesia*, **31**, 185–92 (1952)
10. Li, T. H., Jacobs, B. R., Aviado, D. M., Jr., and Schmidt, C. F., *J. Pharmacol. Exptl. Therap.*, **104**, 149–55 (1952)
11. Marsh, D. F., *J. Pharmacol. Exptl. Therap.*, **105**, 299–316 (1952)
12. Price, H. L., Conner, E. H., Elder, J. D., and Dripps, R. D., *J. Appl. Physiol.*, **4**, 629–35 (1952)
13. Wnuck, A. L., Norton, S., Ellis, C. H., and deBeer, E. J., *Anesthesiology*, **14**, 367–75 (1953)
14. Hampton, L. J., Little, D. M., Jr., and Fuller, E. M., *Anesthesiology*, **14**, 382–89 (1953)
15. Ottolenghi, R., Manni, C., and Mazzoni, P., *Current Researches Anesthesia & Analgesia*, **31**, 243–50 (1952)
16. von Dardel, O., and Thesleff, S., *Current Researches Anesthesia & Analgesia*, **31**, 250–57 (1952)
17. Green, R., *Anaesthesia*, **8**, 52–54 (1953)
18. Organe, G. S. W., *Current Researches Anesthesia & Analgesia*, **32**, 19–22 (1953)
19. Boyan, C. P., and Brunschwig, A., *Surgery*, **31**, 829–38 (1952)
20. Asquith, E., *Can. Med. Assoc. J.*, **67**, 421–24 (1952)
21. Saunders, J. W., *Lancet*, **I**, 1286–88 (1952)
22. James, A., Coulter, R. L., and Saunders, J. W., *Lancet*, **I**, 412–16 (1953)
23. Shackman, R., Graber, I. G., Melrose, D. G., and Smith, J., *Anaesthesia*, **7**, 217–22 (1952)
24. Enderby, G. E. H., *Current Researches Anesthesia & Analgesia*, **32**, 1–6 (1953)
25. Ginzburg, L., Sussman, L. N., and Auerhan, H., *Surg. Gynecol. Obstet.*, **92**, 492–93 (1951)
26. Talbot, T. R., Jr., *Surg. Gynecol. Obstet.*, **93**, 411–12 (1951)
27. Friesen, S. R., Harsha, W. N., and McCroskey, C. H., *Surgery*, **32**, 620–29 (1952)
28. Bromage, P. R., *Lancet*, **II**, 10–15 (1952)
29. Nicholson, M. J., Sarnoff, S. J., and Crehan, J. P., *Anesthesiology*, **14**, 215–25 (1953)
30. Sadove, M. S., Wyant, G. M., and Gleave, G., *Anaesthesia*, **8**, 175–81 (1953)
31. Magill, I. W., Scurr, C. F., and Wyman, J. B., *Lancet*, **I**, 219–20 (1953)
32. Sarnoff, S. J., Goodale, W. T., and Sarnoff, L. C., *Circulation*, **6**, 63–73 (1952)
33. Assali, N. S., and Suyemoto, R., *Am. J. Obstet. Gynecol.*, **64**, 1021–36 (1952)

34. McCubbin, J. W., and Page, I. H., *J. Pharmacol. Exptl. Therap.*, **105**, 437–42 (1952)
35. Assali, N. S., Douglass, R. A., Jr., and Suyemoto, E., *Circulation*, **8**, 62–66 (1953)
36. Kennedy, F., Somberg, H. M., and Goldberg, B. B., *J. Am. Med. Assoc.*, **129**, 664–67 (1944)
37. Kennedy, F., Effron, A. S., and Perry, G., *Surg. Gynecol. Obstet.*, **91**, 385–98 (1950)
38. Michelsen, J. J., *Neurology*, **2**, 255–59 (1952)
39. Dripps, R. D., and Vandam, L. D. (In press)
40. Dripps, R. D., and Vandam, L. D., *J. Am. Med. Assoc.*, **147**, 1118–21 (1951)
41. Dripps, R. D., Lamont, A., Eckenhoff, J. E., Vandam, L. D., and Dumke, P. R., *Organization and Procedures of the Department of Anesthesiology*, 55–57 (College Offset Press, Philadelphia, Pa., 127 pp., 1953)
42. Winkelman, N. W., *Neurology*, **2**, 284–91 (1951)
43. Griffith, H. R., *Current Research Anesthesia Analgesia*, **31**, 367–71 (1952)
44. Cole, F., *Anesthesiology*, **13**, 407–15 (1952)
45. Orner, O., *Acta Chir. Scand., Suppl.*, 167 (1952)
46. Rosenbaum, H. E., Long, F. B., Jr., Hinchey, T. R., and Trufant, S. A., *Arch. Neurol. Psychiat.*, **68**, 783–90 (1952)
47. Eckenhoff, J. E., Elder, J. D., Jr., and King, B. D., *Am. J. Med. Sci.*, **223**, 191–97 (1952)
48. Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D., *Anesthesiology*, **13**, 242–46 (1952)
49. Fraser, H. F., Wikler, A., Eisenman, A. J., and Isbell, H., *J. Am. Med. Assoc.*, **148**, 1205–07 (1952)
50. Bornstein, M., Yorburg, L., and Johnston, B., *J. Am. Med. Assoc.*, **151**, 908–10 (1953)
51. Chase, H. G., Boyd, R. S., and Andrews, P. M., *J. Am. Med. Assoc.*, **150**, 1103–04 (1952)
52. Wikler, A., Carter, R. L., Fraser, H. F., and Isbell, H., *Federation Proc.*, **11**, 402 (1952)
53. Wilson, G., Rupp, C., and Wilson, W. W., *J. Am. Med. Assoc.*, **140**, 1076–79 (1949)
54. Hayes, J. O., *Current Researches Anesthesia & Analgesia*, **32**, 213–15 (1953)
55. Ostlere, G., *Trichlorethylene Anesthesia* (Williams & Wilkins Co., Baltimore, Md., 99 pp., 1953)
56. Nowell, W. K., Stephen, C. R., and Searles, P. W., *Arch. Surg.*, **66**, 35–46 (1953)
57. Pickrell, K. L., Stephen, C. R., Broadbent, T. R., Masters, F. W., and Georgrade, N. G., *Plastic and Reconstructive Surg.*, **9**, 345–54 (1952)

RADIOACTIVITY

BIOLOGIC EFFECTS OF IONIZING RADIATIONS[1]

By Egon Lorenz

Laboratory of Biophysics, National Cancer Institute,[2] Bethesda, Md.

AND

Charles C. Congdon

*Argonne National Laboratory, Division of Biological and
Medical Research, Lemont, Ill.*

It is not intended to cover in this review all the literature on radiobiology which has been published from the beginning of 1952 to the present. It is intended rather to summarize critically some phases of experimental research in which considerable progress has been made recently and which may lead eventually to a better understanding of the processes involved in irradiation injury and its prevention, in the induction of experimental leukemia, and in the irradiation treatment of experimental tumors.

The Role of Specific Ionization in Irradiation Injury

Ionizing radiations, whether they originate from atomic nuclei or are produced by machines, interact with living matter by energy loss along their path. This energy loss or absorbed energy is caused by the production of "ion pairs," and by molecular excitation followed by dissociation into free radicals, atoms, and ions. This mechanism holds for charged particles, such as electrons, protons, α-particles, etc. as well as for electromagnetic radiations such as x- and γ-radiation and for the uncharged neutron. In the course of the ionization process an electron is removed from a neutral molecule and this molecule will assume a positive charge. The ejected electron forms a negative ion by attaching itself to a neutral molecule. The number of such ion pairs in a unit path length (e.g., one μ) is called the "specific ionization." The greater the velocity of a given particle or the greater the energy of a quantum of electromagnetic radiation the less is the specific ionization. For x-radiation in the therapeutic range (200 Kv) the mean specific ionization is 80 ion pairs, for γ-radiation of RaC, 15 ion pairs, for α-particles (disintegration of radon) the specific ionization is 3700 ion pairs. Still higher values have been obtained for fission products. The difference in specific ionization results in striking quantitative differences in biologic effects on cells, viruses, bacteria, or seeds [c.f. Gray (1)]. Qualitative differences are not anticipated because the fundamental process of ionization is the same for all radiations.

The conclusions which can be drawn from the effects of radiations of different specific ionization on single cells, viruses, etc. cannot be transferred to the effects of radiations of different specific ionizations on animals. In experiments of Hollcroft & Lorenz (2) in which the 30 day LD_{50} of mice was compared for internally administered alpha emitters (radon and its short-lived decay products) and x-irradiation it was found that the energy dose of x-irradiation was 1.42 times that of α-particles. Considering the nonuniform distribution of the α-particle dose in comparison to the uniform distribution of the x-radiation dose these results seem to indicate that the biologic effect of the two radiations on mice depends on the total number of ionizations rather than on specific ionization. No conclusions can be drawn from these data with regard to radiations having intermediate or even higher specific ionization. Recent data, however, of Clark et al. (3) who compared the 30 day LD_{50} for mice exposed to fast neutrons (intermediate specific ionization) or γ-radiation from Co^{60} show that one n unit of fast neutrons is equivalent to 4.4 r of Co^{60} γ-radiation, under the conditions of the experiment at the 50 per cent lethality dose [c.f. Zirkle (4)]. More experiments, however, are necessary to evaluate the role of the specific ionization in irradiation injury. This is of considerable importance in arriving at the desired permissible exposure dose of various ionizing radiations for human subjects.

LETHAL IRRADIATION INJURY

As we have seen, the primary action of ionizing radiations consists of formation of ion pairs and molecular excitation which leads to dissociation into free radicals and atoms resulting in destruction of enzymes, denaturation of proteins, etc. The ionization or molecular excitation occurring either within a biologically important molecule or on its surface (e.g., protein or enzyme molecule) is called the "direct action." Ionization and excitation of the water in the organism may give rise to the formation of free radicals, H^+ and OH^- that can react with protein molecules or other acceptors in the medium. This is called the "indirect action" and since large biologic entities contain a high percentage of water this action of the irradiation is of prime importance in the biologic effect as these radicals will react with protein and enzyme molecules within or outside the cell.

On account of the discreet, nonuniform nature of the absorption process and differences in radiosensitivity, in an animal body exposed to total body irradiation, some cells will be killed, others damaged, and some left intact. Usually, death in a mammal exposed to many times the 100 per cent lethal dose will not occur until several days have passed. Death is caused by the primary effects only insofar as they provoke a series of secondary reactions such as pancytopenia, with overwhelming infection, and intractable hemorrhage. In view of recent findings it is highly improbable that the secondary reactions following irradiation are caused by a circulating toxin or the necro-hormones of Caspari (5). Recent experiments by Williams (6) show that in total body irradiation of rats, in which a loop of the small intestine was

shielded, the intestinal mucosa of the shielded loop showed normal epithelium even if the body dose was increased to 1500 r which is 100 per cent lethal. The modification of irradiation injury after total body irradiation by bone marrow injection after exposure, which will be discussed later, also makes it improbable that circulating toxins after irradiation could be the cause of the secondary reactions. If such toxins were present they would prevent modification of the injury by destruction of the injected bone marrow.

When the acute total body dose is increased and the number of animals that die from the irradiation within 30 days are determined, an "S" shaped curve is obtained by plotting percentage of deaths versus dose. The time interval of 30 days is chosen because animals rarely die from acute injury beyond this period. The 30 day LD_{50} varies greatly from species to species [c.f. Cronkite & Brecher (7)]. The 30 day LD_{100} begins at a dose approximately 50 per cent higher than the 30 day LD_{50}. Even for doses many times the LD_{100}, e.g. 10,000 r, the animals usually do not die for about three days, and only for still higher doses death may occur during irradiation. Above 10,000 r convulsions and periods of extensive rigidity and hypothermia are observed in the guinea pig (8).

In the following paragraph we shall deal only with the dose range up to the beginning of the 30 day LD_{100}. In this range, death can be prevented by various means as will be discussed later. As mentioned, death is mainly caused by pancytopenia, with overwhelming infection, and intractable hemorrhage. While usually all three factors contribute to death in some of the species one or the other is predominant. In mice, as Miller et al. (9) have shown, bacteremia is the predominant factor; in other species such as dog, rabbit, and guinea pigs, hemorrhage predominates. The guinea pig is expecially interesting because bacterial invasion following acute lethal exposures was not observed by us. When mice of the C3Hf strain are exposed to a 100 per cent lethal dose of 900 r, bacterial invasion into many organs and tissues is observed beginning with the third day after irradiation and nearly all the mice die with bacteremia (10). This invasion is characterized by an inflammation without leukocytic infiltration. If mice given 900 r total body irradiation are given daily injections of streptomycin, death is delayed: nevertheless, all mice die in the 30 day period and in those dying late, hemorrhages into organs and tissues are observed (11).

The invading organisms are those that exist normally in the intestinal tract; they probably invade through the damaged epithelium of the small bowel even though this epithelium regenerates within 73 hr. after a lethal dose of irradiation [c.f. Williams et al. (12)].

As mentioned above, in many species death from pancytopenia with hemorrhages into organs and tissues is observed following an acute dose of lethal irradiation. This hemorrhagic syndrome is characterized by an erythrocyte count in the neighborhood of one million, a platelet count of 10,000 or less, and a severe leukopenia with increasing tendency of bleeding into organs and tissues. The onset of the anemia is usually abrupt within a few

days, in spite of the fact that erythrocytes are radioresistant and have a life span of the order of 100 days or more. While Allen *et al.* (13) proposed that a heparin like factor was responsible for the bleeding tendency, Jackson *et al.* (14) could not find conclusive evidence that anticoagulants take part in the hemorrhagic syndrome. Whole blood clotting time generally increases during the hemorrhagic syndrome especially in dogs (15). On the other hand, experiments by Lorenz (16) on acutely and chronically irradiated guinea pigs have shown that clotting time in irradiated guinea pigs does not vary significantly from that of normal animals. Admittedly, the capillary determination of clotting time is crude but the results at least show that there is no excessive increase in time of clotting. In recent years the following factors have come to light which at least partially explain the hemorrhagic syndrome. Ross *et al.* (17) found that following massive doses of irradiation large numbers of erythrocytes were found in the lymph of rats and dogs, possibly attributable to endothelial damage, reaching their peak in rats 9 to 14 days and in dogs 11 to 17 days after irradiation. As the hemorrhagic syndrome is accompanied by a decrease of the number of circulating platelets to values of 10,000 or less, Jackson *et al.* (15) studied prothrombin utilization and its relation to platelet counts and whole blood clotting time in dogs and found a striking correlation. Subsequently, Cronkite *et al.* (18) found that injection of massive doses of a platelet suspension in dogs reversed the coagulation defect and prevented hemorrhage. Finally, Woods *et al.* (19) showed that suspensions of platelets introduced intravenously into lymph cannulated dogs (9 to 12 days after a total body irradiation to an LD_{50} or greater) eliminated large scale diversion of erythrocytes into the lymph during the hemorrhagic phase. In addition, the bloody lymph cleared within a few hours. The authors conclude that their studies support the thesis that platelets are essential to maintain vascular integrity and that platelet deficiency is the main cause of the hemorrhagic state.

Although these experiments indicate that the hemorrhagic syndrome could be explained by thrombopenia, however attractive such a hypothesis may be, apparently other factors may also be involved. Lorenz & Congdon (20) found persistently that in experiments with guinea pigs irradiated with an LD_{100} and given bone marrow injections postirradiation (to be discussed later) no hemorrhagic syndrome was observed, although platelet levels reached a low of 10,000 or less 5 to 6 days after irradiation. On the other hand, guinea pigs irradiated to the same dose without bone marrow injection showed similar platelet counts and the hemorrhagic syndrome. The quality of the platelets in the two groups was not studied. While in most cases the hemorrhagic syndrome after a lethal dose will account for the death of the animals, occasionally animals die apparently either with no or a minimum hemorrhagic syndrome; yet the counts of the cells of the circulating blood are comparable with those animals dying with a pronounced hemorrhagic syndrome.

The status of our knowledge of the postirradiation pancytopenia and

hemorrhagic syndrome may be summarized as follows: the abrupt onset of postirradiation anemia can, in part, be explained by the appearance of red cells in the lymphatic system caused by irradiation damage to the vascular bed and by frank bleeding into tissues and organs. One other factor, as yet not evaluated, may be hemolytic in nature as evidenced by the fact that occasional animals do not show any or a minimal hemorrhagic syndrome; yet, the precipitous decrease in the number of circulating erythrocytes is similar in animals with and without the hemorrhagic syndrome.

The hemorrhagic syndrome including the diversion of red cells into the lymphatic vessels can be prevented to a large degree by massive platelet injection, indicating that platelets seem to be essential in maintaining vascular integrity. However, here also other factors may be involved, as postirradiation bone marrow injection prevents the hemorrhagic syndrome and diversion of red cells into the lymphatics. On the other hand, no improved survival was obtained by the platelet injection as eventually all animals died of bacterial infection [Brecher & Cronkite (21)].

MODIFICATION OF IRRADIATION INJURY

Investigations of methods to modify or prevent irradiation injury are of paramount importance. They will lead to a better understanding not only of the primary phenomena that lead to the injury or death, but also may bring practical methods for combatting the injury in man, and may lead to improved techniques in the irradiation treatment of cancer. It is necessary, however, to point out that all such methods will only prevent or ameliorate the acute phase of the injury. Late effects, such as shortening of life span, cataract, or induction of tumors will not be prevented (22). The only exception is the induction of lymphoid tumors in mice which will be discussed in a subsequent chapter.

The preventive measures can be divided broadly into two classes: (a) those that act in reducing the primary injury or, in other words, act as though they neutralize a certain percentage of the dose given; and (b) those preventives which do not alter the extent of primary injury but which stimulate the hematopoietic tissues into rapid recovery that is not observed in nontreated irradiated animals. Furthermore, they also prevent bacterial infection and hemorrhage to a large degree.

(a) The first class of protective measures has been discussed recently in detail by Patt (23) and Ord & Stocken (24). Briefly, this group includes the following procedures: the injection of certain reducing substances, e.g., cysteine or reduced glutathione into animals prior to the irradiation, the injection of anoxia-producing substances such as nitrates or cyanides, or the production of a state of anoxia by providing the animals with an atmosphere of low oxygen tension (approximately 5 per cent), and irradiation of the animals in the anoxic state. As attractive as the hypothesis may be that cysteine and reduced glutathione are oxidized by the radicals formed by the irradiation of the water content of the body, thus removing part of the radicals, it

has not been proven yet. The mechanism of the protection by anoxia is better understood. As the fluids in the body contain dissolved oxygen which may combine with the water radicals to form HO_2 and H_2O_2 thought to react with biologic matter, a reduction of this dissolved oxygen should also have the effect of alleviating the irradiation injury. However, a precise biochemical interpretation is not yet possible. There are many other substances which will protect; they all have in common with those mentioned that they protect only when given prior to or in the case of reduced oxygen tension during irradiation and are ineffective when given afterwards. This is easily understood if it is considered that the primary irradiation damage is induced by the action of the radicals on the biologic matter of the organism. If these mediating substances are to be effective they must be present during the lifetime of these radicals. However, the average lifetime of the radicals formed from water is probably only a small fraction of a second.

(b) Contrariwise, the second class of methods will not be effective when applied prior to irradiation because they are biological in nature and they are subject to radiation damage like the tissues of the host. The principal methods are: spleen protection during irradiation or injection of suspension of splenic tissues postirradiation, injection of bone marrow and parabiosis postirradiation. Probably parabiosis during irradiation with the parabiotic animal shielded would also be effective, but no experimental data are available. The stimulus to investigations of postirradiation protection came from the observation of Jacobson et al. (25), that mice which had been injected with 2 μc. of radiostrontium[89] showed no anemia although the radiostrontium was deposited shortly after injection in the bone with subsequent marked reduction of hematopoiesis in the bone marrow. They found on the other hand that the spleens of such animals, in which little if any radiostrontium was deposited, showed extensive erythropoiesis and megakaryocytopoiesis. They concluded that in spite of the damage produced on bone marrow by the radiostrontium the spleen was able, by its hematopoietic capacity, to take over the function of the damaged bone marrow. They proved this conclusion by exposing mice to total body radiation with the surgically exteriorized spleen shielded by lead [Jacobson et al. (26)]. Doses exceeding almost twice the 30 day LD_{50}, usually 100 per cent lethal, gave excellent survival of the spleen shielded mice. They found abundant hematopoiesis not only in the shielded spleen but also found early recovery of the damaged bone marrow with concomitant recovery of the picture of the circulating blood even though up to 4 to 5 days after irradiation the blood picture was indistinguishable from that of nonspleen shielded mice.

Using the spleen shielding techniques Jacobson and his associates (27) studied subsequently in numerous experiments the mechanism of postradiation recovery. Their observation, that recovery of lymphatic tissue in the intestine of spleen-shielded mice paralleled the recovery of hematopoietic tissue elsewhere, led to the postulation of a humoral basis for the mechanism of recovery from irradiation injury. They observed some protection from

irradiation with liver, intestine, head and thigh shielding; none was observed with kidney shielding. All, however, were inferior to spleen shielding. The larger the volume of shielded spleen, the higher the percentage of survivors and the larger the dose for which enhanced survival was noted. When the pedicle of the shielded spleen was clamped off during irradiation and then released afterwards the animals recovered in the same manner as those in which the pedicle had not been clamped. Clamping of the pedicle without shielding did not promote survival of irradiated mice. When the shielded spleens (either clamped or intact during irradiation) were removed from 5 min. to 2 days after irradiation, recovery of the animals was promoted. Lorenz *et al.* (28) showed that shielding was less effective in immature mice than in adult animals. Further work by Jacobson (27) showed that if during total body irradiation the spleen was also exposed to a portion of the total body dose and then shielded, survival was still promoted. He felt that such studies demonstrated the fixed, more radioresistant reticulum cells to be more.important than the other more radiosensitive precursors of red and white blood cells which would be destroyed by the dose given to the spleen.

The efficacy of spleen protection in causing survival of irradiated mice could be enhanced by pretreatment of the mice with estrogens or cysteine. It was further shown that pretreatment with cysteine plus post irradiation intraperitoneal spleen transplantation also gave an additive effect on survival (27).

In dealing with other species, spleen shielding has been shown to enhance survival in irradiated rats but not in rabbits (27). It is possible that the blood forming abilities of the spleen of the species irradiated determines the success of spleen shielding.

After the demonstration that postradiation transplantation of spleens was protective in irradiated mice (27) it was shown that spleen homogenates (29) and spleen cell suspensions (30) were effective intravenously or intraperitoneally. Since the spleens of mice contain abundant blood forming cells it was natural to try the effect of bone marrow on irradiated animals. Lorenz *et al.* (31, 32) showed that bone marrow could cause survival of irradiated mice and guinea pigs. It has subsequently been demonstrated for rats (33) and hamsters (34). Bone marrow suspensions have been most effective by intravenous and intracardiac routes, less effective by intraperitoneal, intrasplenic, and intrathoracic routes, and not effective when given subcutaneously or intramuscularly. In addition to preventing death from acute total body irradiation, bone marrow suspensions reduced mortality from intravenously administered radon (30) and prevented death in a high percentage of guinea pigs receiving a limited exposure of total-body chronic γ-irradiation until they developed a severe anemia. The majority of animals exposed under the same conditions not receiving bone marrow died of pancytopenia (30).

Postradiation parabiosis has been shown to reduce mortality of the irradiated parabiont by Brecher & Cronkite (35). Removal of the spleen or

adrenal glands in the nonirradiated parabiont did not prevent the protective action of parabiosis (36). Other postradiation procedures have been tried. Salisbury *et al.* (37) indicated the ability of exchange transfusions to promote survival of irradiated dogs. Subsequent work by Leonards *et al.* (38) did not confirm these findings although repeated exchange transfusions temporarily raised the white count of the irradiated dogs to normal levels. Perfusion of blood from irradiated dogs through a normal spleen and then back into the irradiated dog did not enhance ultimate survival. Suspensions of cells from nearly every tissue in the mouse have been tested for their effect on survival after total-body irradiation (39). Other than spleen and bone marrow, only thymus has shown indications of effectiveness. The results with thymus were not reproducible in every experiment and the effectiveness of this tissue remains uncertain (30). Recently it was found that cortical bone given intraperitoneally would enhance survival of the irradiated mouse (20). Both rat and mouse bone were effective in irradiated mice.

Suspensions of cells from several different types of transplantable neoplasms were tried but the only one tested that would cause recovery from the irradiation injury was a reticulum cell sarcoma (30).

The mechanism of postradiation protection of animals by such techniques as spleen and bone marrow transplantation, parabiosis, etc., has been explained in several ways. The idea that the introduced cells of the bone marrow could go to the tissues, the regeneration of which is stimulated, and by their growth could cause an anatomical and functional repopulation of the structure does not seem reasonable in the sense that it could be the only or even a major factor in causing survival. The major factor is probably a humoral one which stimulates regeneration of the hematopoietic system and will be discussed in detail later.

Another possible factor to be considered has been "that the undamaged marrow or spleen serves as a focus for sufficient hematopoiesis to support life until the irradiated but relatively radioresistant marrow reticulum can reconstitute hematopoiesis elsewhere" (40). Such an explanation fails to account for the results obtained using reticulum cell sarcoma suspensions. It has further been shown as discussed previously that mice exposed to a dose which kills 100 per cent in 30 days have a delay in the mean lethal time when treated simultaneously by antibiotics (11).

HUMORAL FACTOR(s)

The hypothesis of a humoral rather than cellular factor in protection from irradiation injury was first proposed by Jacobson (27). The indirect evidence for such a factor was based mainly upon two experiments: (a) splenectomy of the irradiated spleen 5 min. after irradiation still gave some protection to animals irradiated with a lethal dose; and (b) transplantations of immature mouse spleens intraperitoneally into rabbits after irradiation caused earlier recovery of the hematopoietic tissues than in nontreated irradiated controls. Lorenz & Congdon (30) came to the same conclusion from

their experiments. They could show that a reticulum cell sarcoma suspension gave good protection. Guinea pig bone marrow injected into irradiated mice also gave protection though sporadic. They explained the success or failure in their experiments in the following way. The amount of the humoral factor produced by the living cells may be very small, but its presence may be needed until the damaged marrow of the host begins to recover. In homologous transplants, the marrow stays alive and can be found in intraperitoneal transplants many weeks after irradiation. In heterologous guinea pig marrow transplants into irradiated mice, the transplanted marrow cells stay alive for several days but the production of the humoral factor will diminish as the heterologous cells die. It is probably pure chance that in the successful experiments a sufficient number of cells may have stayed alive longer thus producing the unknown factor sufficiently long enough to aid recovery. Finally it was shown (41) that rat bone marrow will probably stay alive in the intraperitoneal cavity of irradiated mice much longer than guinea pig bone marrow. Subsequently rat bone marrow injection gave persistently reproducible results in protecting mice against irradiation injury. The phenomenon of heterologous growth of transplanted tissues into irradiated animals is well known.

The interesting work of Cole *et al.* (42) tries to show that the nuclei of cells of the immature spleen contain an active principle which causes survival when spleen homogenates are given to irradiated mice. Using a fractionation technique of differential centrifugation in sucrose media they obtained subcellular fractions of splenic cells.

Cole *et al.* (42) estimated that a homogenate derived from spleen would contain 4 per cent intact cells. The nuclear fraction of this homogenate (equivalent to about 280 mg. of immature spleen injected into each mouse) was thought to contain even fewer whole cells, although cell counts of the fraction were not made as in the case of whole homogenate. However, it has been shown that 15 mg. of adult spleen cell suspensions injected intravenously into mice of the same genetic derivation exposed to 900 r, 70 per cent to 100 per cent survival can be obtained (39). It is quite possible but has not been tested that lesser amounts of living cells might give a measure of protection for a dose of 750 r (as used by Cole *et al.*), in view of the finding of Lorenz, *et al.* (32) that bone marrow suspensions containing 1.5 mg. or less of wet bone marrow are highly effective. Stoner & Hale (43) reported that a piece of spleen 1 mm. in diameter transplanted intraocularly would enhance survival from total-body irradiation. It may further be pointed out that if the humoral factor should be a nucleoprotein then the specific one that is active must not be present in any significant amount in most tissues since radiation protection can be demonstrated only for certain hematopoietic tissues and related elements (39).

Recently Cole & Ellis (44) reported that ribonuclease did not destroy the activity of the spleen homogenate and its nuclear fraction but that trypsin and desoxyribonuclease did destroy it. They concluded that the humoral

agent is a desoxyribonucleoprotein. If this work can be confirmed a great
deal has been accomplished in radiation protection studies.

IRRADIATION INDUCTION OF LYMPHOID TUMORS

Since the discovery that total-body irradiation will induce lymphoid
tumors in mice by Krebs *et al.* (45), the systematic research of Kaplan on the
irradiation induction of lymphoid tumors in C57 black mice has confirmed
older work and greatly advanced the knowledge of the factors involved that
govern the induction of this tumor. The most important of these factors are:
lymphoid tumors induced by total-body irradiation tend to originate mono-
centrically in the thymus and disseminate later to other organs and tissues;
thymectomy prevents this disease (46). Fractionated irradiation at intervals
of 4 to 8 days gives greater incidence and shorter time of tumor development
than daily fractionation to the same total dose (47). Irradiation of part of
the body, either the upper half or the lower half to the same integral dose
as in total-body irradiation effectively prevented the induction of lymphoid
tumor. Only if the upper and lower half of the body are irradiated alternat-
ingly at intervals of 1 or 6 or 24 hr. lymphoid tumors were induced; if the
interval was extended to 4 days, no tumors were induced (48). Shielding with
lead one thigh of mice exposed to total-body irradiation inhibited the induc-
tion of lymphoid tumors (49). Concomitantly with thigh shielding Kaplan
and Brown noted that thymus weight returned more rapidly to normal than
in mice the thighs of which were not shielded during total-body irradiation.
Observation of the modification of irradiation injury by spleen protection
and postirradiation bone marrow injection, discussed in the previous chapter,
suggested that prolonged depression of hematopoietic tissues may play an
important role in the induction of lymphoid tumors. Both procedures result
in a rapid recovery of hematopoietic tissues of mice given total-body ex-
posures. In the experiments of Kaplan and Brown where the thigh was
shielded, bone marrow was protected which should have an effect on the
recovery of hematopoietic tissues similar to that of injection of homologous
bone marrow or spleen protection. This was shown by Lorenz *et al.* (50)
in experiments in which three groups of C57 black mice were irradiated.
The first and second group received 225 r total-body exposure at weekly inter-
vals to a total dose of 900 r. The first group served as control group without
spleen protection. In the second group, the spleen was exteriorized and pro-
tected by lead during all four exposures. The third group received a single
total-body exposure of 900 r with spleen protection. Lymphoid tumor inci-
dence 300 days after irradiation was begun, amounted to 70 per cent in the
first group in which the spleen was not protected; 2 per cent in the second
group in which the spleen was protected; and 0 per cent in the third group in
which the spleen was protected. In nonirradiated control animals, the lymph-
oid tumor incidence is 6 to 8 per cent (47). The circulating lymphocytes
show a prolonged depression lasting approximately 100 days in the nonspleen

protected group while this depression is less pronounced and of shorter dura-
tion in the spleen protected animals. These results indicate that the preven-
tion of lymphoid tumor induction following spleen protection during irradia-
tion is caused by an unknown factor in the bone marrow or in the spleen
which stimulates the rapid recovery of lymphoid structures; or in other
words prolonged hypoplasia of bone marrow and lymphoid structures favors
induction of lymphoid tumors.

Similar results were obtained by Kaplan & Brown (51). They exposed
C57 black mice to 4 doses of 168 r at 8 day intervals. Lymphoid tumor inci-
dence was 87 per cent in the group that received no bone marrow. It de-
creased to 33 per cent in the group that was given bone marrow suspension
intravenously and to 3 per cent in the group, the thigh of which was shielded.
As the thymus in both of the latter groups rapidly recovered its weight they
reached the conclusion that the acceleration of thymic recovery by bone
marrow injections or thigh shielding effectively diminishes or prevents
lymphoid tumor induction. They explain the difference between the effective-
ness of endogenous and exogenous bone marrow as most likely to be caused
by the time lag the exogenous bone marrow requires to start proliferating.

Bone marrow apparently also plays a role in spontaneous mouse lymphoid
tumors. Hybrid mice obtained by crossing of a nonleukemic strain with a
leukemic strain develop a considerable spontaneous incidence of lymphoid
tumor, though less than the incidence in the leukemic strain. If the hybrids
are given a single intravenous injection of bone marrow obtained from one
month old animals of the leukemic strain, a significantly earlier and greater
incidence of lymphoid tumors is observed. However, if the hybrids are given
a single intravenous injection of bone marrow of one month old animals of the
nonleukemic strain lymphoid tumor incidence is delayed and decreased (53).

The question arises whether or not the synergistic or inhibitory action
of certain hormones in irradiation induced leukemia can also be explained by
a depression or stimulation of the irradiated bone marrow. Kirschbaum et al.
(52) found a synergistic action of x-irradiation and estrogenic hormone in
accelerating the onset of induced lymphoid tumors. Patt et al. (54) found that
estrogen induces a leukopenia 10 to 14 days after injection. It is therefore
possible that the synergistic effect of estrogen in irradiation induced lymph-
oid tumor may be explained by an enhancement and prolongation of the
irradiation induced depression of hematopoietic tissues. On the other hand,
testosterone, according to Kaplan & Brown (55) inhibits lymphoid tumor
induction but only when given simultaneously with x-irradiation. The mech-
anism of this inhibitory action is not known. Finally, cortisone will signifi-
cantly decrease induction of lymphoid tumors by irradiation when injections
are started simultaneously with irradiation or delayed until 6 weeks after
irradiation. The mechanism of this inhibition is also not known but it seems
likely that it does not act by stimulation of the damaged irradiated bone
marrow, as even a decrease in survival rates of mice given total-body irradia-

tion of 410 r and 0.25 mg. of cortisone daily after irradiation was found (56). Adrenalectomy significantly increases induced lymphoid tumor incidence (57).

The induction of lymphoid tumors in mice caused by total-body irradiation seems to be a peculiarity of this species with the possible exception of the rat (58). Congdon & Lorenz (59) studied leukemia incidence in several hundred inbred and hybrid guinea pigs, both irradiated and nonirradiated controls, and came to the conclusion that acute x-irradiation or chronic γ-irradiation are at present not established as leukemogenic agents for this species.

Explosions of atomic bombs, however, apparently cause leukemia by the massive γ-irradiation of high energy associated with them. In Hiroshima and Nagasaki the increase is highly significant at present in subjects exposed at distances less than 2000 m. and the magnitude of increase in leukemia is an inverse function of the distance from the hypocenter. The disease occurred mostly in the early intermediate age groups and the predominant types were acute myelocytic leukemias [c. f. Furth & Lorenz (60)].

IRRADIATION TREATMENT OF EXPERIMENTAL TUMORS

From a purely physical point of view, it seems hopeless to attempt to destroy a tumor by irradiation even if great differences in radiosensitivity exist between tumor and surrounding tissues. The physical reason for this is that the absorption process of radiation is of discrete nature, i.e., not uniform. Therefore we cannot expect to kill each tumor cell even if large doses are given. Yet, it is known that a permanent regression of certain tumors can be obtained by irradiation. Radiologists stress the importance of the tumor bed in radiation therapy; and it is assumed that the effects of irradiation on the vascular supply of the tumor contributes in no small measure to the observed regression of many neoplasms. It has been claimed that in cases of lymphoid tumors, irradiation treatment directed to a localized area is associated with tumor regression in distant sites of the body. This has led to the suggestion that there may be a systemic effect of the irradiation treatment.

Hollcroft et al. (61) showed the existence of a pronounced systemic effect in the treatment of experimental transplanted lymphoid tumors in mice. They used a localized tumor which kills the host mice in 30 to 40 days. If the animals carrying the tumor were given total-body irradiation of 400 r the tumor became impalpable and in approximately 20 per cent of the animals permanent regressions were obtained. With spleen protection or postirradiation bone marrow injections, the total-body dose to the tumor bearing animals could be increased to 800 r resulting in permanent regressions ranging from 30 to 90 per cent in different experiments. On the other hand, 4000 r given to the tumor alone in a single dose resulted only a few per cent of permanent regressions (62).

The question arises whether or not these systemic effects exist only in the irradiation treatment of lymphoid tumors or hold for all types of tumors.

Recent investigations by Hollcroft & Matthews (63) show that the same phenomenon is observed also with transplanted mammary tumors. It is, however, not as pronounced as with lymphoid tumors because the mammary tumors are considerably more radioresistant than the lymphoid tumor used. Of special practical interest is their finding that a small total body dose of 50 r given simultaneously with a tumor dose of 1000 r is sufficient to give a maximum systemic effect i.e., a tumor regression exceeding by far the effect of tumor irradiation alone with single doses up to 6000 r.

The synergistic factor or factors act only in total-body irradiation; when the tumor is shielded and the remainder of the body irradiated no tumor regression is observed. Some synergism does occur, however, if the tumor and body are irradiated at different times. The maximum synergism occurs in simultaneous irradiation of body and tumor. It apparently gives rise to a series of unknown reactions that disappear in time. This is not in contradiction to the finding that no synergistic effect was observed when the circulation to the tumor was clamped off during irradiation. Apparently, free circulation is necessary at all times for the action of the synergistic factor.

The nature of the synergistic factors is obscure. In additional experiments, Hollcroft et al. (64) studied factors modifying tumor regression. At present it is not possible to state whether or not these factors are the same as in simultaneous tumor and body irradiation.

When tumor bearing animals were deprived of food and water 24 hr. prior to and during irradiation, statistically significant greater reduction of tumor size occurred than in normal animals exposed to the same tumor dose. In acutely starved animals the blood sugar content is very low. As glucose protects animals from irradiation death (65), lack of glucose can conceivably increase irradiation damage to the tumor.

As hydrogen peroxide is formed by irradiation of water, it is likely that it also plays a role in the irradiation effects on animals. Intravenous injection of hydrogen peroxide within a minute of the start of the irradiation gave a significantly greater tumor regression than in normal tumor bearing animal exposed to the same tumor dose (64). While hydrogen peroxide most likely does not remain as such after injection, it may start a chain of events of short duration in the tumor similar to the synergistic factors in simultaneous tumor and body irradiation. It may also result in a higher content of dissolved oxygen in the body fluids. This was tested by exposing the tumor bearing mice to an atmosphere of 95 per cent oxygen and 5 per cent carbon dioxide two minutes prior to and during irradiation. A five-fold increase in tumor regression was noted in these hyperoxic animals in comparison to animals breathing room air and exposed to the same dose (64). On the other hand in anoxic animals breathing 92 per cent nitrogen and 8 per cent oyxgen little tumor regression was observed. This agrees with findings of Dowdy et al. (66) that anoxia protects animals from irradiation death.

Although the findings that hyperoxia has a profound effect on tumor regression were made on a lymphosarcoma, they may hold for other tumors

also. They indicate that radioresistance of a tumor may at least in part be caused by a more or less pronounced state of anoxia of the tumor. A state of anoxia is easily visualized especially in a rapidly growing lymphoid tumor in which the blood supply cannot keep pace with growth resulting in areas of necrosis in large tumors. Therefore, by decreasing tumor anoxia in saturating body fluids with oxygen, radiosensitivity can be enhanced without materially changing radiosensitivity of normal tissues as these already have sufficient oxygen available. It is also well known that tumors become apparently radio-resistant after repeated x-irradiation treatments. The general consensus of opinion is that this increase radioresistance is probably casued by the survival of radioresistant cells following repeated irradiations so that the tumor finally consists predominantly of radioresistant cells. It also has to be considered that each irradiation may tend to diminish the blood supply to the tumor, therefore increasing its radioresistance by anoxia; however, no experimental data are available yet, whether or not hyperoxia will increase radiosensitivity in tumors which have become "radioresistant by repeated irradiations.

Modern radiotherapy has made great strides in recent years in improving physical methods of tumor treatment by the use of x-radiation in the million volt range and the use of rotational techniques (67). It must be realized, however, that improvements of physical methods alone, although of utmost importance, will only improve the cure rate up to a certain limit. This limit is mainly given by the differential of tumor radiosensitivity to normal tissue sensitivity. The urgent need is felt not only for vigorous experimental research in changing this differential but also in applying some of the results discussed in the foregoing to clinical radiotherapy.

LITERATURE CITED

1. Gray, L. H., *Brit. Med. Bull.*, **4**, 11–18 (1946)
2. Hollcroft, J. W., and Lorenz, E., *J. Natl. Cancer Inst.*, **12**, 533–44 (1952)
3. Clark, J. W., Vogel, Jr., H. H., and Jordan, D. L., *Argonne National Laboratory, ANL-4948*, 32–37 (1953)
4. Zirkle, R. E., *Radiation Biology*, **1**, Hollander, A., Ed., McGraw-Hill Book Co., Inc., New York, N. Y. (In press)
5. Caspari, W., *Deut. med. Wochschr.*, **49**, 269–71 (1923)
6. Williams, Jr., R. B. (Personal communication, September, 1953)
7. Cronkite, E. P., and Brecher, G., *Ann. Rev. Med.*, **3**, 193–214 (1952)
8. Andrews, H. L., and Brace, K. C., *Federation Proc.*, **12**, 6 (1953)
9. Miller, C. P., Hammond, C. W., and Tompkins, M., *J. Lab. Clin. Med.*, **38**, 331–43 (1951)
10. Williams, Jr., F. P., and Congdon, C. C., *Argonne National Laboratory, ANL-4840*, 17–23 (1952)
11. Congdon, C. C., and Lorenz, E. (Unpublished data)
12. Williams, Jr., R. B., and DeLong, R. P., *Federation Proc.*, **12**, 406 (1953)
13. Allen, J. G., Sanderson, M. M., Kirschon, A., and Jacobson, L. O., *J. Exptl. Med.*, **87**, 71–86 (1948)

14. Jackson, D. P., Cronkite, E. P., Leroy, G. V., and Halpern, B., *J. Lab. Clin. Med.*, **39**, 449–61 (1952)
15. Jackson, D. P., Cronkite, E. P., Jacobs, G. J., and Behrens, C. F., *Am. J. Physiol.* **169**, 208–17 (1952)
16. Lorenz, E., *J. Chemie et Physique*, **48**, 264–74 (1951)
17. Ross, M. H., Furth, J., and Bigelow, R. R., *J. Hematology*, **7**, 417–28 (1952)
18. Cronkite, E. P., Jacobs, G. J., Brecher, G., and Dillard, G. H. L., *Am. J. Roentgenol. Radium Therapy*, **67**, 796–803 (1952)
19. Woods, M. C., Gamble, F. N., Furth, J., and Bigelow, R. R., *Blood*, **8**, 545–53 (1953)
20. Lorenz, E., and Congdon, C. C. (Unpublished data)
21. Brecher, G., and Cronkite, E. P., *Proc. N. Y. Pathol. Soc.*, 116–18 (1951); (Personal communication, September, 1953)
22. Lorenz, E., Schweisthal, R., and Congdon, C. C., *Argonne National Laboratory, ANL-4948*, 12–14 (1953); (Unpublished data)
23. Patt, H. M., *Physiol. Revs.*, **33**, 35–76 (1953)
24. Ord, M. G., and Stocken, L. A., *Physiol. Revs.*, **33**, 356–36 (1953)
25. Jacobson, L. O., Simmons, E., and Block, M. H., *The Univ. of Chicago, CH-3886* (1946)
26. Jacobson, L. O., Marks, E. K., Gaston, E. O., Robson, M., and Zirkle, R. E., *Proc. Soc. Exptl. Biol. Med.*, **70**, 740–42 (1949)
27. Jacobson, L. O., *Cancer Research*, **12**, 315–25 (1952)
28. Lorenz, E., Jacobson, L. O., Uphoff, D., Sutton, H., Schweisthal, R., *Argonne National Laboratory, ANL-4451* (1950)
29. Cole, L. J., Fishler, M. C., Ellis, M. E., and Bond, V. P., *Proc. Soc. Exptl. Biol. Med.*, **80**, 112–17 (1952)
30. Lorenz, E., and Congdon, C. C., *Proc. Fourth International Congress of Hematology* (Mar del Plata, Argentina, September, 1952, In press)
31. Lorenz, E., Uphoff, D., Reid, T. R., and Shelton, E., *J. Natl. Cancer Inst.*, **12**, 197–201 (1951)
32. Lorenz, E., Congdon, C. C., and Uphoff, D., *Radiology*, **58**, 863–77 (1952)
33. Chamberlain, R. H., *Radiology*, **58**, 877 (1952)
34. Smith, W. S., Marston, R. A., and Gonsbery, L., *Proc. of the Radiation Research Society Meeting* (State Univ. of Iowa, Iowa City, Iowa, June, 1953)
35. Brecher, G., and Cronkite, E. P., *Proc. Soc. Exptl. Biol. Med.*, **77**, 292–94 (1951)
36. Finerty, J. C., Binhammer, R. T., Butler, J. K., Schneider, M., and Walker, C. R., *Federation Proc.*, **12**, 43 (1953)
37. Salisbury, P. E., Rekers, P. E., Miller, J. R., and Marti, N. F., *Science*, **113**, 6–7 (1951)
38. Leonards, J. R., Heisler, C. R., Buckaloo, G. W., Lavik, P. S., and Friedell, H. L., *Proc. of the Radiation Research Soc. Meeting* (State Univ. of Iowa, Iowa City, Iowa, June, 1953)
39. Congdon, C. C., and Lorenz, E., *Argonne National Laboratory, ANL-4948*, 18–20 (1953)
40. Storer, J. B., Lushbaugh, C. C., and Furchner, J. E., *J. Lab. Clin. Med.*, **40**, 355–66 (1952)
41. Congdon, C. C., and Lorenz, E., *Am. J. Physiol.* (In press)
42. Cole, L. J., Fishler, M. C., and Bond, V. P., *U. S. Naval Radiological Defense Lab. Rept.*, *USNRDL-378* (1952)

43. Stoner, R. D., and Hale, W. M., *U. S. Atomic Energy Commission Documents, BNL-1401* (1952)
44. Cole, L. J., and Ellis, M. E., *Proc. Radiation Research Society Meeting* (Univ. of Iowa, Iowa City, Iowa, June, 1953)
45. Krebs, C., Wagner, A., and Rask-Nielson, H. C., *Acta Radiol. Suppl.*, **10**, 1–53 (1930)
46. Kaplan, H. S., *Acta Union Internat. contre le Cancer*, **7**, 850–59 (1952)
47. Kaplan, H. S., and Brown, M. B., *J. Natl. Cancer Inst.*, **13**, 185–208 (1952)
48. Kaplan, H. S., and Brown, M. B., *J. Natl. Cancer Inst.*, **12**, 427–36 (1951)
49. Kaplan, H. S., and Brown, M. B., *Science*, **116**, 195–96 (1952)
50. Lorenz, E., Congdon, C. C., and Uphoff, D., *J. Natl. Cancer Inst.*, **14**, 291–302 (1953)
51. Kaplan, H. S., and Brown, M. B., *J. Natl. Cancer Inst.*, **14**, 303–16 (1953)
52. Kirschbaum, A., Shapiro, J. R., and Mixer, H. W., *Cancer Research*, **13**, 262–68 (1953)
53. Lorenz, E., Law, L., and Congdon, C. C. (Unpublished data)
54. Patt, H. M., Straube, R. L., Tyree, E. B., Swift, M. N., and Smith, D. E., *Am. J. Physiol.*, **159**, 269–80 (1949)
55. Kaplan, H. S., Brown, M. B., *Cancer Research*, **12**, 445–47 (1952)
56. Ellinger, F., *Proc. Soc. Exptl. Biol. Med.*, **80**, 214–17 (1952)
57. Kaplan, H. S., Brown, M. B., and Marder, S. N., *Cancer Research*, **11**, 262–63 (1951)
58. Metcalf, R. G., and Inda, F. A., *U. S. Atomic Energy Commission Document, UR 88* (1951)
59. Congdon, C. C., and Lorenz, E., *Am. J. Pathol.* (In press)
60. Furth, J., and Lorenz, E., *Radiation Biology*, **1**, (Hollander, A., Ed., McGraw-Hill Book Co., Inc., New York 18, N. Y., in press)
61. Hollcroft, J., Lorenz, E., and Hunstiger, H., *J. Natl. Cancer Inst.*, **11**, 1–16 (1950)
62. Hollcroft, J., Lorenz, E., Congdon, C. C., and Jacobson, L. O., *Proc. Fourth Inter-American Congress of Radiology* (Mexico City, Mexico, November, 1952, in press)
63. Hollcroft, J. W., and Matthews, M., *J. Natl. Cancer Inst.* (In press)
64. Hollcroft, J. W., Lorenz, E., and Matthews, M., *J. Natl. Cancer Inst.*, **12**, 751–63 (1952)
65. Bacq, Z. M., *Experientia*, **7**, 11–19 (1951)
66. Dowdy, A., Bennett, L. R., and Chastain, S. M., *Radiology*, **55**, 879–89 (1950)
67. Wheatley, B. M., Steed, P. R., Savage, E. W., King, J. H., Forster, E. W., Hodt, H. J., Jones, I. R., and Smithers, D. W., *Brit. J. Radiology*, **26**, 57–72 (1953)

LABORATORY AIDS TO DIAGNOSIS AND THERAPY[1]

By Gardner Middlebrook

National Jewish Hospital and the University of Colorado School of Medicine,
Denver, Colorado

A survey of the literature reveals that a few decades ago there were intense interest in, and extensive efforts to discover, a serologic test for tuberculosis. It was early recognized that tuberculous infection was so ubiquitous in most parts of the world that the tuberculin skin test was of little or no value in distinguishing the "infection" from the "disease." Indeed, the infection is still so widespread that the skin test with tuberculin can be expected to do little more than separate the exposed and infected individuals from the as yet uninfected members of the population. Recently there has been a revival of interest in the possibility of applying certain newly-developed serologic methods to the differentiation of the "infected" from the "diseased." Therefore, it seems timely that a review be made of this field.

The Phenomena of Hemagglutination and Conditioned Hemolysis

In 1948, Keogh, North & Warburton (1) observed that certain polysaccharides of bacterial origin would absorb onto red cells and render the red cells agglutinable by specific antibodies against the adsorbed polysaccharides. Middlebrook & Dubos (2) applied this principle to the study of experimental tuberculosis, showing that sheep red cells exposed to certain extracts or products of the culture filtrates of tubercle bacilli could sensitize red cells to agglutination in the sera of tuberculous animals and human beings.

Muniz (3, 4), Fisher & Keogh (5), and Middlebrook (6) independently observed that if complement, in the form of fresh guinea-pig serum, were added to the complete hemagglutination system, the hemagglutination reaction could be transformed into a hemolytic ("conditioned hemolysis") reaction: the red cells were lysed in the presence of complement when specific antibodies reacted with the specific antigen adsorbed to the surface of the red cells. Thus, in effect, red cells behave in these tests as a convenient agent for the demonstration of an antigen-antibody reaction. In fact, it has been shown that the hemolytic test (conditioned hemolysis) can detect amounts of antibodies against certain antigens which are not demonstrable by any other known serologic technique (7).

Boyden & Suter (67) have suggested the term "hemosensitin" for those antigens which adsorb spontaneously onto red cells and render the red cells sensitive to agglutination (or lysis) by antibody against the adsorbed antigen. This new term would seem useful to distinguish such substances from those which directly cause agglutination of red cells, such as certain hemagglutinating viruses.

[1] The survey of the literature pertaining to this review was completed in August, 1953.

Boyden (8) has demonstrated another serologic method, related in some respects to the phenomenon of direct adsorption of bacterial products onto erythrocytes: he showed that certain proteins, including a protein from the tubercle bacillus, would adsorb onto erythrocytes which had previously been treated with tannic acid, and thus render the cells agglutinable by specific antiprotein sera.

Many investigators have sought to determine the mechanism of adsorption of bacterial antigens onto red cells (9 to 24). Unfortunately, very little is known concerning the physicochemical aspects of this problem. Neter & Zalewski (47) have shown that certain electrolytes must be present in solution for an *Escherichia coli* hemosensitin to adsorb onto red cells. It has also been observed that serum or the albumin fraction of serum will inhibit hemosensitin adsorption (7). It is of some interest, furthermore, that (7) even after reaction with antibody the tubercle bacillus polysaccharide complex will still adsorb onto red cells, rendering them susceptible to lysis by subsequent addition of complement: this fact may be interpreted as evidence that the "conditioned hemolysis" reaction can be utilized to demonstrate "univalent," nonprecipitating antibody against the polysaccharide antigen in the tubercle bacillus hemosensitin.

Purified protein fractions from tubercle bacilli as well as certain, probably degraded, polysaccharide fractions are apparently unable to adsorb onto red cells (7, 11). On the other hand, evidence has been presented that either a special polysaccharide complex or a polysaccharide-protein complex in tuberculin can adsorb onto red cells and permit detection of antibodies against either the polysaccharide I of Seibert or against certain protein fractions of tubercle bacilli, distinct from that fraction which will adsorb onto red cells previously treated with tannic acid (7).

It has generally been observed that the hemolytic test is more sensitive for the detection of antibodies than is the hemagglutination test (12). Although there is good qualitative correspondence between the two reactions, hemagglutination and hemolysis, in the case of the tubercle bacillus antigen-antibody systems there is evidence that the hemolytic reaction is the more sensitive for the detection of certain anti-polysaccharide antibodies than is the hemagglutination reaction (7). Furthermore the comparative ease and clarity with which the hemolytic reaction can be observed gives this modification some superiority in practical use over the hemagglutination reaction (7, 12). Indeed, it is this author's experience that large scale application of the hemagglutination reaction is prohibited by the fact that each tube must be shaken and carefully studied with a hand lens for accurate results, whereas whole racks of tubes of the hemolytic test may be read at one glance in mass-survey studies: positively reacting sera may be immediately identified and submitted to more precise quantitative analysis.

Gernez-Rieux & Tacquet (12, 25) have written two excellent reviews in French on the phenomena of hemagglutination and "conditioned hemolysis."

Boyden's phenomenon of presensitization of red cells with tannic acid for

the adsorption of tubercle protein has not yet been applied in clinical investigations.

CLINICAL APPLICATIONS

The results of clinical applications of hemagglutination reactions by different investigators are summarized in Table I. Although much use has been made of the hemagglutination and hemolytic reactions in experimental laboratories in the study of experimental tuberculosis in animals, it is immediately evident from examination of the table presented that the results obtained clinically leave a margin of error too great to permit the hemagglutination test to be of any significant diagnostic value.

TABLE I

RESULTS REPORTED ON CLINICAL APPLICATIONS OF THE HEMAGGLUTINATION TEST

Authors	Tuberculous patients (In per cent)	Apparently healthy individuals (In per cent)	Nontuberculous diseases (In per cent)
(21)	92*	0	0
(44)	80	7‡	0†
(23)	53	0†	17
(63)	80	7	4
(64)	66	14	0†
(40)	63	20‡	18
(57)	95	3	—
(53)	55	13‡	—
(65)	56	10	—
(55)	69	30	—

* Percentage of individuals who gave positive reactions.
† Too few cases to be statistically significant.
‡ Tuberculin skin-test-negative subjects.

However, it is equally clear that the discrepancy in the results obtained by different groups of investigators must be attributed as much to difference in materials and techniques in performing the hemagglutination test as to differences in the estimation of the clinical status of the patients from whom the sera were drawn.

Table II summarizes the results obtained on clinical application of the hemolytic test. In particular, the striking discrepancy should be noted in the results obtained in the same laboratory at different times (26, 27). Gernez-Rieux & Tacquet (12) have made the most extensive study yet reported on the incidence of positive reactions in the hemagglutination and "conditioned hemolysis" tests as they were performed in their laboratories. In summary, they have pointed out that the incidence of false positive reactions in these tests is much lower in children aged 5 to 12 years than in adults, obtaining excellent results in children: approximately 5 per cent "false positives" and

TABLE II

RESULTS REPORTED ON CLINICAL APPLICATION OF THE HEMOLYTIC TEST

Authors	Tuberculous patients (In per cent)	Apparently healthy individuals (In per cent)	Nontuberculous disease (In per cent)
(54)	76*	—	13*
(12)†	73	9†	—
(42)	45	10‡	20‡
(65)	82	32§	—
(26)	94	0	4
(27)	not given	7	—
(66)	50	1.5	—

* Percentage of individuals who gave positive reactions.

† Same authors as reference (54), but with use of a different "hemosensitin" preparation.

‡ Too few cases to be statistically significant.

§ Tuberculin skin-test negative subjects.

92 to 95 per cent "true positives" in those with "active" tuberculosis. They emphasized the high incidence of positive reactions in children with primary infections. Also, using the hemagglutination test, they attempted to correlate the evolution of the disease in human beings with serologic titre changes, having demonstrated in experimental animals that chemotherapy with streptomycin had a definite effect on the titres in experimental animals. They were not able to demonstrate any significant parallelism between the changes in titre in these tests and the evolution of the tuberculosis in human beings under the influence of different methods of therapy, nor were they able to relate titres, except in the most general fashion, with the red-cell sedimentation rate, the flocculation reaction of Vernes' (28), or the classical complement fixation tests of Besredka and of Calmette and Massol (29). Other investigators have confirmed these conclusions (22, 30 to 38).

It may be said that, in general, old chronic tuberculosis is more commonly associated with negative reactions than is the case with recently diseased individuals. Also, it can certainly be stated that a negative reaction in either the hemagglutination or the hemolytic test cannot be considered an index of cure or of the disappearance of the living tubercle bacilli in the host. On the other hand, positive serologic reactions may be obtained in these tests with the sera of tuberculous patients after all evidences of "active" tuberculous disease, as judged by other criteria, have disappeared. This is interpreted variously by different authorities. There is no doubt that the persistence of circulating antibody does not necessarily indicate persistently "active" disease in tuberculosis any more than it does in typhoid, brucellosis, or other infectious diseases.

Several investigators have studied the effect of BCG vaccination on these tests. Gernez-Rieux & Tacquet (12) observed that approximately 50 per cent of vaccinated individuals developed significant increases in titre between the second and sixth months after vaccination, and that the antibodies, detected by the hemagglutination technique, did not persist. Smith & Scott (39) observed a rise in titre in 75 per cent, four months after BCG vaccination. Fleming *et al.* (40) observed results similar to those of Gernez-Rieux & Tacquet (25). Levy (41) has made similar observations. Thus, BCG vaccination in man, unlike the results that have been observed in experimental animals (12), does not give rise to more than 50 per cent "positive" reactions in these tests, regardless of the methods of vaccination thus far studied.

It has been emphasized (42, 43) that laboratory workers although apparently healthy and remaining so for some periods of time at least, often show positive reactions in these tests as a result of frequent exposure to tubercle bacilli which are unable to cause progressive clinical disease.

Comparison of the incidence of positive reactions in the hemagglutination test in healthy human beings has shown a higher percentage of positive reactions in tuberculin-skin-test-positive than in tuberculin-skin-test-negative subjects. Thus some of the supposedly "false-positive" reactions may be attributable to mild infections resulting from repeated exposure to tubercle bacilli without the development of clinical disease.

It is important to emphasize the fact that (44, 66) skin-testing with tuberculin can give rise to antibodies detectable in these tests: in the experience of the author these antibodies do not persist for longer than six to eight weeks. Hall (31) has shown that large doses of old tuberculin injected into experimental animals can give rise to highly positive reactions in these tests; and it is certain that several groups of investigators have failed to take this fact into consideration in their interpretation of their results. Many investigators have implicitly assumed that the antibodies detected by these serologic reactions may be "protective" antibodies with some relationship to the state of specific acquired resistance of the host against tuberculosis. There is no evidence to support this assumption; indeed, Hall's observation (31) that old tuberculin can give rise to these antibodies is sufficient to rule out this possibility: injections of old tuberculin do not confer specific acquired resistance against tuberculosis on any host, regardless of the species of host.

Scott & Smith (44) have emphasized that the terminal stage of fatal tuberculosis is often associated with a low or falling titre of antibodies.

It is pertinent to report here some veterinary studies in which these serologic tests have been applied. Sohier *et al.* (45), Gernez-Rieux & Tacquet (12), and Fisher & Gregory (46) have shown the incidence of positive reactions in tuberculous cattle to be higher in those suffering from visceral tuberculosis than in those with isolated lymphatic lesions, positive reactions being obtained in 85 to 90 per cent of cases with active visceral disease, the

incidence of positive reaction in normal cattle in the hemolytic test having been very low in terms of the arbitrary dividing line which was selected to define the "false" and the "true" positive reaction titres.

To be precise, the hemagglutination and hemolytic tests with antigen or antigens from tubercle bacilli as "hemosensitin" should probably be designated "serologic tests for certain mycobacterial antigens." Rothbard (21) first directed attention to the fact that antigens of mycobacteria other than tubercle bacilli could inhibit the specific hemagglutination reaction when old tuberculin from tubercle bacilli was used to sensitize the red cells. Several other investigators (9, 12, 43) have demonstrated cross-reactions between different mycobacterial antigens in these tests. Indeed, cross-reactions between tubercle bacilli and *Mycobacterium para-tuberculosis* (Johne's bacillus) have permitted attempts at application of these tests to the diagnosis of Johne's disease in cattle (48). Furthermore, cross-reactions between tubercle bacilli and Hansen's bacilli have permitted application of these tests for the diagnosis of leprosy in human beings (22, 49, 50). Here again, however, the incidence of "false positive" reactions in normal individuals has defeated the widespread application of these tests to the diagnosis of these myco-bacterial diseases.

METHODS AND TECHNIQUES

The red cells.—Several investigators have studied the usefulness of different concentrations of red cells for the performance of the hemagglutination and hemolysis reactions. A concentration of 0.5 per cent (final) has commonly been used (2, 6, 42, 55), although other investigators (10, 26, 55) have used higher and lower concentrations without detectable disadvantage. The use of modified Alsever's solution for the preservation of sheep's blood as a source of red cells with constant sensitivity to agglutination, or to lysis by complement over long periods of storage has found by far the widest application. However, red cells from species other than sheep have been studied. Boyden (51) first showed that the red cells of different species of animals vary in their susceptibility to sensitization by bacterial antigens. Gernez-Rieux & Tacquet (12) have compared hemagglutination titres obtained with the red cells of sheep, human beings (group O), rabbits, guinea pigs, horses, cattle, and chickens. They observed variation in intensity of agglutination with red cells from these different species, human red cells in general agglutinating less strongly than sheep red cells. Sohier *et al.* (52), however, obtained excellent results with the use of human red cells (Group O) in the hemagglutination reactions. Of particular importance is the observation of Adcock *et al.* (53) that red cells from sheep, after repeated blood-drawings, may be difficult to saturate with the normal anti-sheep-red-cell agglutinins in human serum in the absorption of such serum, which is a necessary preliminary step in performance of these tests.

It has been pointed out (6), and repeatedly confirmed by other investigators, that human red cells in Group O are not so satisfactory for use in the

hemolytic test as are sheep red cells, because of the relative resistance of human red cells to lysis by complement. Although Sievers *et al.* (23) had difficulties in the adsorption of sera with normal sheep red cells, other investigators have observed a very low incidence of human sera which could not be freed of natural anti-sheep-red-cell-antibodies by the procedure originally described (2).

The antigens.—Specially-prepared aqueous extracts of tubercle bacilli were first used for red-cell sensitization (2). It was also found that certain old tuberculin preparations possessed high activity in sensitizing red cells. Scott & Smith (44) and Rothbard *et al.* (56) used a four-times concentrated old tuberculin (Lederle). Brodhage (57) studied several different tuberculin preparations. Sohier *et al.* (52), Gernez-Rieux & Tacquet (12), and Lucentini & Boisvert (42) have studied the tuberculin prepared by Bretey & Lamensans (58), called IP 48. Starting with this tuberculin and using a fractionation technique based upon the original preparation of active extracts from tubercle bacilli, Lamensans *et al.* (13) have shown that a product containing less than 0.42 per cent nitrogen and consisting mostly of polysaccharide is the most active agent in tuberculin for sensitizing red cells for specific hemolysis; this has been confirmed (7). Thus, attempts at standardization of different tuberculin preparations for use in skin-tests (43) by comparative studies of their ability to sensitize red cells for the hemagglutination or hemolytic reactions would seem not to be feasible. For example, a tuberculin which is very active in skin-hypersensitivity tests, Seibert's PPD, has very little activity in sensitizing red cells to hemagglutination or hemolysis in specific sera (12, 31, 59).

Although the preliminary observations of Brodhage (57) suggested that tuberculins derived from different types of tubercle bacilli, human or bovine, might be used in these tests to differentiate infections attributable to the different types, this possibility has not been confirmed.

The only serologic cross-reaction between Mycobacteria and other microorganisms which has been discovered by means of these reactions is a cross-reaction between Staphylococci and tubercle bacilli, first observed by Rothbard (60). This observation has been confirmed by Maillard & Gagliardo (27) as well as by this author. Indeed, some studies have indicated (27) that preliminary absorption of test sera with staphylococci assists greatly in distinguishing true positive from false positive reactions in the hemolytic test. The author has observed that different preparations of tuberculin from the same laboratory may contain different amounts of this staphylococcus-cross-reacting antigen, and that this antigen may be chemically separated from the specific red-cell-sensitizing fraction of tuberculin (61).

Of some immunologic interest is the fact that the antigène-méthylique of Nègre and Boquet, commonly used in the past in serologic tests for tuberculosis, does not sensitize red cells for specific serum hemagglutination or hemolysis, nor does it cross-react with the antigens of tubercle bacilli which are adsorbed onto red cells from tuberculin (12).

The discrepancies in results reported by different investigators in clinical applications of these serologic tests may, in large part, be attributed to differences in the antigens used in different laboratories to sensitize the red cells. It does not seem unlikely that further study of the antigens involved will permit greater serologic specificity for these reactions.

Technical details.—Gernez-Rieux & Tacquet (12) have exhaustively reported on the techniques which have been used in the performance of the hemagglutination and hemolytic reactions. They have shown the optimal temperature for red-cell sensitization to be 37°C. for 2 hr. for both the hemagglutination and hemolytic ("conditioned hemolysis") reactions, and that the pH of the electrolyte solution in which the red cells are sensitized can be varied widely without significant effect on the hemagglutination or hemolytic titres obtained with the use of the differently-treated red cell suspensions.

The original recommendation for incubation of sensitized red cells, test serum, and complement before reading the results in terms of hemolysis was 1 hr. at 37°C. (6). Maillard & Gagliardo (26) have modified this recommendation, employing a preliminary period of refrigeration at 4°C. for 1 hr. This recommendation has proved (61) to increase the sensitivity of the hemolytic test without decreasing its specificity. This improvement in sensitivity is consistent with Schaefer's (62) observation that the tubercle-bacillus-polysaccharide-antibody complex fixes complement much more efficiently in the cold than at 37°C.: there is no doubt that the antibodies most commonly appearing in the sera of tuberculous human beings and detectable by the hemolytic test are antibodies against the polysaccharide I of Seibert, as indicated above.

As with other serologic reactions, the titres defined as positive vary essentially according to the type and technique of serologic reaction used and the antigen employed to sensitize the red cells. It has been the general experience with all investigators that, with the same test, the same antigens, and the same techniques, there is a definite constancy of the titre obtained in untreated tuberculous patients: titre variations greater than twofold are only rarely observed. Furthermore, tuberculous patients' sera, heat-inactivated at 56°C. for 30 min., and preserved with thimerosal-N.F. (merthiolate) at 4°C., manifest constant activity in the hemolytic test over periods of many months. It remains to be seen whether or not this same constancy is manifested by "positive" sera from nontuberculous individuals. No studies of this problem have been reported.

GENERAL COMMENTS

A critical review of the literature on the hemagglutination and hemolytic tests reveals that these tests are applicable to experimental animal studies, but that neither test deserves widespread routine clinical application. In view of the fact that the hemolytic test, even in the hands of the most experienced investigator (12), while giving 80 to 85 per cent positive reactions in patients with tuberculosis, yielded some 8 to 10 per cent of positive reac-

tions in nontuberculous individuals. Although it be admitted that no sero-logic test for any disease gives 100 per cent positive reactions in individuals suffering from that disease, and no reactions in individuals not suffering from that illness, the high instance of false positive reactions in the hemagglutina-tion and hemolytic tests for mycobacterial antibodies would seem to pre-clude their widespread clinical usefulness. However, further studies of the antigens used to sensitize the red cells and the nature of the reactive sub-stances often present in the sera from human beings who are skin-test-negative to tuberculin, may permit the simpler and more precisely quanti-tative hemolytic test to have diagnostic value.

LITERATURE CITED

1. Keogh, E. V., North, E. A., and Warburton, M. F., *Nature*, **161,** 687–88 (1948)
2. Middlebrook, G., and Dubos, R., *J. Exptl. Med.*, **88,** 521–58 (1948)
3. Muniz, J., *Newsletter Soc. Am. Bact.*, 9 (Rio de Janeiro, Brazil, January, 1 1950)
4. Muniz, J., *Fifth Intern. Congr. Microbiol.* (Rio de Janeiro, August 17–24, 1950)
5. Fisher, S., and Keogh, E. V., *Nature*, **165,** 248 (1950)
6. Middlebrook, G., *J. Clin. Invest.*, **29,** 1480–85 (1950)
7. Middlebrook, G., *Bull. N. Y. Acad. Med.*, **28,** 7, 474–75 (1952)
8. Boyden, S., *J. Exptl. Med.*, **93,** 106–20 (1951)
9. Fisher, S. V., *Australian J. Exptl. Biol. Med. Sci.*, **29,** 1–8 (1951)
10. Fisher, S., *Australian J. Exptl. Biol. Med. Sci.*, **28,** 613–18 (1950)
11. Grabar, P., Boyden, S., Tacquet, A., and Borduas, A., *Compt. rend.*, **234,** 899–901 (1952)
12. Gernez-Rieux, C., and Tacquet, A., *Progr. Exploration Tuberc.*, **5,** 66 (1952)
13. Lamensans, A., Grabar, P., and Bretey, J., *Compt. rend.*, **232,** 1967–69 (1951)
14. Adler, F. L., *Proc. Soc. Exptl. Biol. Med.*, **74,** 561–65 (1950)
15. Avezzu, G., and Schiesaro, N., *Arch. "E. Maragliano" patol. e clin.*, **6,** 347–54 (1951)
16. Bier, O., *Ann. inst. Pasteur*, **81,** 650–56 (1951)
17. Brodhage, H., *Beitr. Klin. Tuberk.*, **107,** 494–511 (1952)
18. Gard, S., *Acta Pathol. Microbiol. Scand. Suppl.*, **91,** 107–14 (1951)
19. Gernez-Rieux, C., and Tacquet, A., *Bull. acad. méd.* (*Paris*), **133,** 556 (1949)
20. Iland, C. N., *J. Pathol. Bact.*, **63,** 735–41 (1951)
21. Rothbard, S., *Med. Clin. N. Amer.*, **35,** 603–14 (1951)
22. Shoji, H. (Personal communication, 1952)
23. Sievers, O., Ulstrup, J., and Winblad, S., *Nord. Med.*, **43,** 667–69 (1950)
24. Hein, H., and Sroka, W., *Ann. Tuberc.*, (*Nara, Japan*), **3,** 107–12 (1953)
25. Gernez-Rieux, C., and Tacquet, A., *Ann. inst. Pasteur, Lille*, **4,** 17–104 (1951)
26. Maillard, E. R., and Gagliardo, F. J., *Am. Rev. Tuberc.*, **64,** 675–81 (1951)
27. Maillard, E. R., and Gagliardo, F. J., *Am. Rev. Tuberc.*, **66,** 762–64 (1952)
28. Vernes, A., *Travaux et Publications de l'Institut Prophylactique*, **4,** (N. Maloine, Publishers, Paris, France, 62 pp., 1926)
29. Gernez-Rieux, C., and Tacquet, A., *Ann. inst. Pasteur*, **78,** 550–55 (1950)
30. Lapponi, G., and Lalle, A. M., *Intern. Congr. Clinical Pathol.* (London, England, July, 1951)
31. Hall, W. H., *Bull. Univ. Minn. Hosp. and Minn. Med. Foundation*, **22,** 557–67 (1951)
32. Anderson, H. W., Platou, R. V., and Spatafova, S., *Pediatrics*, **8,** 498–505 (1951)

33. Anderson, H. W., Platou, R. V., and Spatafova, S., *Am. J. Diseases Children*, **83**, 76–78 (1952)

34. Bowen, D. A. L., and Jennings, R. G., *Brit. J. Tuberc.*, **47**, 41–45 (1953)

35. Bunn, P., Drobeck, B., Ginn, J., and Adair, C., *Ann. Internal Med.*, **37**, 84–95 (1952)

36. Hinson, K. F. W., Jones, A. R., and Chamberlin, J. A., *Brit. J. Tuberc.*, **46**, 50–59 (1952)

37. Maher-Loughnan, G. P., and Hilson, G. R. F., *Tubercle*, **33**, 297–303 (1952)

38. Yaoi, H., Takei, M., Maeda, H., and Nishi, H., *Yokohoma Med. Bull.*, **2**, 161 (1951)

39. Smith, D. T., and Scott, N. B., *Am. Rev. Tuberc.*, **62**, 121–27 (1950)

40. Fleming, J. W., Runyon, E. H., and Cummings, M. M., *Am. J. Med.*, **10**, 704–10 (1951)

41. Levy, F. M., *Groupe d'Etude Pour la Vaccination Antituberculeuse. Recherches Immunologiques.* (Travail du Centre International de l'Enfance, Paris, France, 1952)

42. Lucentini, L., and Boisvert, M., *Ann. inst. Pasteur*, **82**, 55–65 (1952)

43. Gaby, W. L., Block, J., and Bandi, A., *Am. Rev. Tuberc.*, **65**, 272–77 (1952)

44. Scott, N. B., and Smith, D. T., *J. Lab. Clin. Med.*, **35**, 303–7 (1950)

45. Sohier, R., Siminitzis, G., and Juillard, J., *Bull. acad. vét. France*, **23**, 393–97 (1950)

46. Fisher, S., and Gregory, T. S., *Australian Vet. J.*, **27**, 25–34 (1951)

47. Neter, E., and Zalewski, N. J., *Bact. Proc.*, **57** (1953)

48. Gernez-Rieux, C., Tacquet, A., Gaumont, R., Verge, J., and Cauchy, L., *Bull. acad. vét. France*, **23**, 465–568 (1950)

49. Levine, M., *Proc. Soc. Exptl. Biol. Med.*, **76**, 171–73 (1951)

50. Gernez-Rieux, C., Montestruc, E., and Tacquet, A., *Ann. inst. Pasterur, Lille*, **4**, 3–17 (1951)

51. Boyden, S. V., *Proc. Soc. Exptl. Biol. Med.*, **73**, 289–91 (1950)

52. Sohier, R., Trimberger, R., and Juillard, J., *Ann. inst. Pasteur*, **79**, 347–50 (1950)

53. Adcock, J., Haley, R. R., and Davey, W. N., *J. Lab. Clin. Med.*, **38**, 736–41 (1951)

54. Gernez-Rieux, C., and Tacquet, A., *Ann. inst. Pasteur*, **81**, 149 (1951)

55. Mollov, M., and Kott, T. J., *Am. Rev. Tuberc.*, **65**, 194–200 (1952)

56. Rothbard, S., Dooneief, A. S., and Hite, K. E., *Proc. Soc. Exptl. Biol. Med.*, **74**, 72–75 (1950)

57. Brodhage, H., *Acta Davosiana*, **4**, 1–14 (1951)

58. Bretey, J., and Lamensans, A., *Compt. rend.*, **232**, 1880–82 (1951)

59. Boulanger, P., and Kenst, H., *Can. J. Public Health*, **43**, 38 (1952)

60. Rothbard, S. (Personal communication, 1951)

61. Middlebrook, G. *et al.* (Unpublished data)

62. Schaefer, W. B., *Ann. inst. Pasteur*, **64**, 301–15 (1940)

63. Gernez-Rieux, C., and Tacquet, A., *Ann. inst. Pasteur, Lille*, **3**, 1–34 (1950)

64. Sohier, R., Juillard, J., and Trimberger, I., *Ann. inst. Pasteur*, **78**, 283–85 (1950)

65. Hall, W. H., and Mannion, R. E., *J. Clin. Invest.*, **30**, 1542–46 (1951)

66. Gerstl, B., Kirsh, D., Andros, E. M., Winter, J. W., and Kidder, L. E., *Am. J. Clin. Pathol.*, **22**, 337–44 (1952)

67. Boyden, S. V., and Suter, W. E., *J. Immunol.*, **68**, 577–89 (1952)

TOXICOLOGY[1]

By Henry F. Smyth, Jr.

Mellon Institute, Pittsburgh, Pennsylvania

In 1950 the eighty-first Congress of the United States appointed the House Select Committee to investigate the Use of Chemicals in Food Products, commonly known as the Delaney Committee. In 1951 the eighty-second Congress broadened the field of investigation to include cosmetics. Public hearings were held on 59 days from 1950 through 1952, and 217 witnesses were heard on the use of chemicals in fertilizers, in production, processing, and distribution of food and in cosmetics. The printed transcript of the testimony occupies 1803 pages, much of it concerned with fact and speculation about toxicology (1). A major revelation of the hearings was the extent of existing doubt of adequate protection of public health afforded by current legal controls upon the use of chemicals. Whether it is justified or not, this attitude emphasizes the growing importance of toxicological investigation performed upon materials expected to reach the general public.

In recognition of the controversy regarding the safety of chemicals in food, the Food and Nutrition Board of the National Research Council established the Food Protection Committee in 1950. The Committee has formulated guiding principles (2) and is seeking to specify adequate procedures to assure the safety of chemicals used in food technology, to assemble and evaluate scientific information and to advise and assist interested parties to ascertain the facts upon questions of safety.

Advances in technology are constantly increasing the number of new materials in preparations handled by the public. New insecticides, fungicides, and rodenticides are increasing the yield from agriculture while herbicides are decreasing the labor required to produce the crops. Fumigants and fungicides are decreasing losses of food during preparation and distribution. New packaging materials are increasing the convenience and safety of retail food distribution. New ingredients are enhancing the palatability, convenience, and attractiveness of prepared foods. New preparations are lightening the burden of housekeeping. New fibers and treatments are changing the texture and comfort of clothing. New cosmetics are simplifying the problem of charm. These are only a few examples of developments which are in the main welcomed by the public. They are to be expected with increasing frequency in the future.

In the number of people potentially affected, the new materials far outweigh for the toxicologist the problems of therapeutic agents which first engrossed him and the problems of industrial environments which next engaged his attention. He must consider the possible effects of a large number

---

[1] The survey of the literature pertaining to this review was concluded in July, 1953.

of new chemicals, used neither under the close observation of a physician who can afford some risk for the sake of curing a disease, nor under careful supervision by a factory worker whose wages and compensation insurance justify some small risk. They are to be handled by the general public at its own whim. The responsibility resting upon the shoulders of the toxicologist may be enormous.

It must be emphasized that the toxicologist can never prove a material to be absolutely safe for indiscriminate human use. His work is restricted to animal experiment and a limited number of confirmatory trials with human volunteers. Work with one species never proves absolutely the response of another species. Only extensive prolonged human use under careful observation for generations can prove safety absolutely. Our social organization makes impossible the control and the time required to conduct such a demonstration of proof. The degree of risk which is tolerable will vary with the need for the new product, but in no case can the degree be expressed in quantitative terms. The toxicologist predicts, by means of animal experiment, using any and all of the medical sciences, how much of a particular chemical can be tolerated by humans and what will be the nature of the results if this tolerance be exceeded. Technologists help him to predict the degree of human contact which will result from a proposed application of the chemical. He and others then weigh the two predictions against benefits to society and decide whether or not the proposal is useful enough to justify the risk. Important factors in the decision are the nature of injury to be expected should the tolerance be exceeded and the benefits which would accrue from adoption of the proposal.

When the toxicology of new products chiefly concerned therapeutic agents, the physician with his intimate knowledge of disease and disability had the primary responsibility for determining that the need for a new agent was sufficient to justify the uncertainties of human safety. When the toxicology of new products began to concern materials used industrially, chemists and engineers became more important in the decision that the need for the product justified the existing degree of uncertainty of safety because they were able to determine the magnitude of the need. Today it is a team of many specialists who must determine whether or not the need for a new material is sufficient to justify the possible risk to health in its use. To an increasing extent it is federal administrators who weigh the need shown by the technologists against the uncertainty of safety shown by the toxicologist to determine that the risk is justified by the probable public good.

Confirmation of safety of the use of a particular material will not be attained short of several years of widespread application. Careful observations should be made during this period, which may be regarded as a trial, to determine whether or not the application is actually safe. Fatalities which may result will normally be reported without special efforts but minor nonspecific effects might not be noticed unless searched for critically. Fowler (3) reported one useful study along these lines. In the Mississippi-Yazoo

Delta area agricultural insecticides have come into use in tremendous volume since about 1947. A survey of the area was made to collect data upon death rates by various causes and upon school attendance records as an index of transient illness, in comparison with those covering the entire State of Mississippi for the years immediately before and immediately after 1947. In some respects the record of the Yazoo Delta area was better than that of the State as a whole. The author concluded that there is no evidence that large use of pesticides has directly or indirectly injured the people of this area. More such studies by qualified epidemiologists will be reassuring that the criteria of safety now being used to interpret animal experiments are in fact sufficient to protect the public health.

Much of today's toxicological study is in the nature of screening to determine quickly and economically whether proposed use of a chemical is clearly unsafe or whether it may be safe enough to justify extensive technological and toxicological investigation. Actually toxicological study is always a step by step operation, and it should be coordinated with other phases of new product development. Each additional bit of evidence that a compound will serve a useful purpose justifies more detailed toxicological investigation, and each new favorable toxicological finding justifies more extended technological study. When the two phases are well coordinated a compound is ready for marketing at the same time that there is available toxicological evidence of safety. The great majority of proposed uses of chemicals are dropped during this step by step operation and never reach the market because of either toxicological or technological objections.

Several deficiencies should be remedied before toxicology can fully meet the need for its services. Further study of efficient methods for detecting adverse response of animals to chemicals is required in order that the large amount of toxicological study demanded by modern technological advances can be thoroughly performed with the facilities available. Further information upon the relationship of human to animal response is urgently needed, and agreement upon the public health significance of animal injuries known not to be predictive of human injuries is also essential. Above all else, however, is the pressing need for basic information upon joint toxic action, the effect of one chemical whose actions may be well known upon the effect of another which is equally well understood when acting alone. The public is exposed to small amounts of many chemicals, each of which may have been shown to be without risk when properly used. Is the total effect the simple sum of all the individual effects or is it less or more than the sum? At present, in the absence of full understanding of joint toxic action, experience has to be relied upon for an answer and extreme caution for protection of public health.

One of the further needs of toxicology is more extensive scientific publication, particularly information about new materials. It is often construed that a toxicological study has served its purpose when it has convinced public officials that a proposed use of a compound is safe and permissible. Publica-

tion may be much delayed or entirely omitted. It would be preferable if the evidence of safety of all new materials reaching the public should be available in the scientific literature to allow general scrutiny by all qualified experts in order to avoid dependence on the judgment of a few. This course would enrich the literature with facts which would certainly be helpful in other fields. Organs of publication are limited in capacity but can be expanded if necessary.

METHODS

Controversy and uncertainty about the safety of additives in food arises from several causes. Foremost is the failure to appreciate that toxicology can establish only probable safety and that absolute safety is an unreal concept. There is lack of unison upon what degree of risk to health is justified and upon what experimental work is called for to reduce the risk to any particular degree. Of only slightly lesser importance is the suspicion, based upon the absence of toxicological results from the literature, that untested materials are being used in foods and are otherwise reaching the public.

The Food Protection Committee (2) has stressed the point of risk or reasonable doubt of safety, and Oser (4) has presented the same question with more discussion. In 1949 Lehman *et al.* (5) writing informally for the United States Food and Drug Administration, outlined the toxicological studies they feel are desirable to investigate the properties of a new material to be added to food. Their outline is being rather generally followed in the United States.

General understanding and acceptance of screening tests will reduce the probability of totally untested materials reaching the public by making it economical to obtain useful, though admittedly incomplete, information on hazards well before the potential economic value of a material justifies extensive study. Nale (6) has outlined the screening methods used for preliminary study to detect the most outstanding hazards. Fassett & Roudabush (7) described a four-week screening test to estimate the degree of chronic toxicity to be expected from prolonged intake of a material.

Beauvillain (8) presented an approach to quantitating chronic toxicity studies which results in an expression for the degree of "chronicity" of a material quite distinct from the degree of toxicity.

Smyth *et al.* (9) pointed out that toxicology can be separated into quantitative and qualitative phases, answering separately the questions of how much will cause any effect and what is the nature of injury from an excess. In studies of quantitative toxicity increased sensitivity is achieved if work is concentrated upon those criteria of effect which are most efficient and which will detect response to the smallest amounts of foreign chemical. As far as is now evident the nonspecific responses such as growth rate and organ weight appear to be the most efficient, detecting adverse effect at a dosage lower than that which will produce more specific anomalies in experimental animals.

McGowan (10, 11, 12) has made an interesting contribution to understanding the fundamental mechanisms of toxicity. On the basis of a large amount of data on acute toxicity for mammals and insects collected from the literature he distinguished two basic types of toxic action, physical and chemical. By means of calculations based on relative solubility and thermodynamic considerations he showed a great uniformity in the effective concentration of many chemicals in an assumed biophase for all mammalian and insect species for which he had data. For these chemicals he concluded that toxicity is caused solely by the presence of the chemical in some body fluid and is quantitatively the same for all species when expressed in terms of concentration. The uniformity in nature among chemicals manifesting physical toxicity consists of their lack of association in solution and their inability to participate in hydrogen bonding. McGowan's work is provocative and calls for extension of such basic considerations to chemical toxicity and to chronic toxicity.

PESTICIDES

The greatest activity in new chemicals reaching the public is in the field of pesticides. This activity is partly attributable to competitive efforts to discover more effective materials and partly attributable to the loss of effectiveness of old materials because insects acquire resistance. Little progress is evident in the goal of highly specific poisons for each pest, desirable in order to reduce hazard to humans. Only a small part of the work on pesticides can be summarized here.

In a series of papers Lehman (13 to 20) has summarized current United States Food and Drug Administration studies on the toxicity of a wide variety of intentional and incidental food additives, stressing pesticides. Patterson & Lehman (21) have brought the series up to date. Scattered through the series are valuable examples of the reasons why a compound may or may not be considered safe for use, such as production of malignancy in some species, slow elimination, or storage in adipose tissue.

Recently cholinesterase inhibitors have been found to be potent insecticides. They all give essentially the same symptoms in mammals. Death results from inhibition of cholinesterase in muscles, leading to respiratory paralysis, anoxia, and terminal convulsions. Atropine is a generalized antidote. Parathion is a cholinesterase inhibitor widely used as an agricultural insecticide. Annis & Williams (22) studying a severe acute poisoning found a fall in serum pH and calcium and a rise in serum potassium and phosphorus. They conclude that cholinesterase inhibition is not the only important mechanism of action of the compound. Small doses detectably reduce the human plasma cholinesterase level and this phenomenon is utilized to protect workers handling parathion by evaluating their exposure in advance of injury. Mountain *et al.* (23) and Gardocki & Hazleton (24) found that *p*-nitrophenol appears in the urine following absorption of parathion, and this metabolite can be used to evaluate exposures too brief or too scant to cause a

reduction in plasma cholinesterase. Lieben *et al.* (25, 26) reported that excretion of *p*-nitrophenol by animals is evident within 24 hr. of a subcutaneous or dermal dose and persists for 32 days or more. A level of 40 μg per 100 ml. may exist without symptoms. Residues upon food do not appear to be a public health problem because parathion is to a large extent decomposed by weathering before the crop is harvested. Barnes & Denz (27) found 10 p.p.m. in the rat diet increased the mortality among pups but was otherwise harmless, but 50 p.p.m. in the diet increased mortality with lesions in the exocrine glands, hypoplasia of spleen, and thymus similar to effects in humans.

Malathon is a new cholinesterase inhibitor which is an effective insecticide whose mammalian toxicity is considerably less than that of parathion. According to Holland *et al.* (28) rats tolerate 1000 p.p.m. in their diet.

Chlorinated compounds represent the majority of the currently used agricultural insecticides, and residues upon foodstuffs must be considered because of the stability of these molecules. It has become increasingly apparent that many of these have the solubility requirements and the chemical stability to be stored for long periods in body fat to be liberated later, perhaps in large amounts, during periods of metabolic stress. Fat storage was first noted for DDT [1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)-ethane], and it is now well recognized that analysis of body fat of any American adult is likely to reveal the presence of this insecticide, as a result of its widespread use and the almost universal presence of traces of residue on marketed products. Recently experimental evidence for fat storage has been reported by Ingle (29) and Ambrose *et al.* (30) for chlordane, Davidow & Frawley (31) for benzene hexachloride, Davidow & Radomski (32, 33) for heptachlor, and Spencer (34) for dilan.

Methoxychlor is another chlorinated insecticide. Hodge *et al.* (35) reported that rats tolerate 200 p.p.m. in their diet for two years without effect and with little accumulation in the tissues while dogs tolerate without effect 300 mg. per kg. per day for a year. This compound is apparently many times as safe as DDT and is an example of small changes in a molecule increasing mammalian safety with little sacrifice of insecticidal effectiveness.

2,4-D (2,4-dichlorophenoxy acetic acid) and 2,4,5-T (2,4,5-trichlorophenoxy acetic acid) are widely used herbicides which reduce hand labor in control of weeds. Their stability is sufficient so that residues may be expected on some marketed crops. Drill & Hiratzka (36) have shown that dogs tolerate long repeated doses of 10 mg. per kg. without effect but that twice this level may be fatal.

Sodium fluoroacetate (1080) is an extremely potent rodenticide which is used under rather rigid controls to prevent public contact. Nevertheless accidental death has resulted. Harrison *et al.* (37) reported on one such victim who died in convulsions with respiratory failure and ventricular fibrillation. The gross pathology was identical to that from sodium fluoride poisoning. Analysis of the cadaver led to the conclusion that at least 6 mg. per kg. had

been ingested. Lindenbaum *et al.* (38) reported the maximum nonlethal dose for a rat to be 1 mg. per kg., and Peters *et al.* (39) found the mechanism of action to be competition in the tricarboxylic acid metabolic cycle leading to production of a fluorotricarboxylic acid which cannot be metabolized further. Chenoweth *et al.* (40) reported glycerol monoacetate is a useful antidote in animals, given intramuscularly without dilution.

Dinitro-*o*-cresol is one of the newer agricultural insecticides, applied by spraying. Parker *et al.* (41) reported that the fatal dose for rats is 25 mg. per kg. but that a near fatal dose repeated in 24 hours produces no greater or less response. They found that an increase in environmental temperature increases the toxicity. Harvey *et al.* (42) fed known amounts to human volunteers and found that 15 to 20 μg. per gm. of blood is the minimum level which causes subjective symptoms. The compound is only slowly excreted, indicating there is cumulative effect from repeated doses. Pollard & Filbee (43) examined exposed agricultural workers and found high blood levels with corresponding objective evidence of absorption in raised metabolic rate, elevated blood urea, and increased nitrogen excretion.

FOOD

In comparison with pesticides, little has been published about the toxicity of intentional food additives and of packaging components which may enter foods. The polyglycol bread softener (polyoxyethylene stearate) which has been the subject of public interest and legal maneuvers in recent years is not now recognized as a legal ingredient in bread in the United States although it was legally used in many millions of loaves for a period of about six years. Little of the extensive toxicological experiment performed upon this material has yet reached the scientific literature. Culver *et al.* (44) has reported that in humans the softener can be completely recovered from urine and feces and therefore it is not metabolized in the body. Harris *et al.* (45, 46) found that 25 per cent of the softener in the rat diet reduced growth and had other effects, and the tolerated level was lower in hamsters. In respect to glycerine monostearate, which is also a bread softener, Reiser *et al.* (47) reported that this material is formed in the digestive tract in large amounts during human digestion of fat and hence may be assumed to be harmless.

Hine *et al.* (48) presented evidence based on two-year feeding to rats that synthetic glycerine is no more toxic than glycerine obtained from natural fats. Fitzhugh *et al.* (49) reported on two-year feeding of synthetic sweetening agents to rats and conclude that sodium cyclohexyl sulfamate and saccharin are much safer than dulcin and P-4000. Smith (50) on the basis of two-year doses to rats found the plasticizers butyl stearate and dibutyl sebacate have a large safety factor when used in plastic food wraps while Devel *et al.* (51) similarly concluded for isopropyl and steryl citrates.

A new manifestation of toxicity from industrial materials to be at least partially elucidated is bovine hyperkeratosis. For over 30 years it has been

known that highly chlorinated naphthalenes can produce a fatal liver injury in humans upon inhalation or absorption by other routes. Upon contact they can cause a skin condition known as chloracne. By control of working conditions, injuries have been almost eliminated among industries using the materials, and injuries among the public are unknown. For over 10 years bovine hyperkeratosis has puzzled veterinarians and the live-stock industry and considerable losses of cattle have resulted. Sikes & Bridges (52) and Bell (53) have now shown that highly chlorinated naphthalenes can cause the condition and that they have reached cattle through the use of industrial greases on the farm. As little as 2.5 mg. per kg. body weight of some compounds eaten over a period of several weeks can be fatal to cattle according to Bell (54). Hansel *et al.* (55) reported that the mechanism of injury appears to be interference with the conversion of carotene to Vitamin A and that it persists for an extended period after the compounds are withdrawn. McEntee & Olafson (56) described changes in the sex glands of cattle which have never been reported for humans. It is evident that cattle are considerably more sensitive to highly chlorinated naphthalenes than are humans.

ATMOSPHERIC POLLUTION

Nothing is definitely known about the possible toxic effects of the very small concentrations of industrial materials and waste products in the air which constitute what we call air pollution. A few acute episodes have demonstrated that their concentration can reach seriously injurious levels under unusual atmospheric conditions. Both their low concentration and their presence in varying combinations has handicapped experimental study of the problem. Cadle & Magill (57) have produced a synthetic smog which to a considerable extent duplicates the eye irritation frequently found in Los Angeles. The components were nitric acid, sulfur dioxide and trioxide, ozone, gasoline, oil, sodium chloride, and lamp black, none of which alone could produce the symptoms. Amdur, Schulz & Drinker (58) and Amdur, Silverman & Drinker (59) have studied sulfuric acid fog in guinea pigs and humans. They find laryngeal spasm is a function of the concentration while lung damage is a function of the time-concentration product. Humans did not detect 0.35 mg. fog per c. m., but reflex responses occurred at this low level. Gray *et al.* (60) studying nitrogen dioxide found as little as 8 p.p.m. four hours a day caused damage to rat lungs and inflammation of the upper respiratory tract, but it was not progressive with longer exposure. Vintinner & Baetjer (61) found that bituminous coal dust or smoke did not increase the susceptibility of rats to lobar pneumonia.

INORGANIC

Several of the rarer metals are now being studied toxicologically for the first time because of their applications in the development of nuclear energy where small numbers of persons may be exposed. Space limitations forbid

further mention of this work. The more familiar inorganic materials are still sources of new toxicological facts.

Despite continued study of cases of pneumonoconiosis and silicosis from a variety of dusts and of continued experimental work, no convincing explanation of the production of silicosis has yet appeared. Clelland et al. (62) found the silica particle to consist of a relatively insoluble core with an outer layer of greater solubility. The soluble layer can be removed in an aqueous buffer at pH 7.5. The same authors (63) found that polishing regenerates the soluble layer, and they suggest it is vitreous silica formed on the crystal surface by frictional work. King et al. (64) found that removal of the soluble layer reduced solubility of the dust to 10 per cent but did not reduce the ability to cause fibrosis. In fact, when the soluble layer was removed with hydrofluoric acid fibrogenesis was enhanced. Policard & Collet (65) found among inhabitants of sandy North Africa deposits of silica in the lungs in periarterial and peribronchial sheaths resembling coal in anthracosis and iron oxide in siderosis. No silicotic lesions are found, and the dust did not cause fibrosis when injected intraperitoneally in the guinea pig. They conclude that either the sand is harmless because it is not freshly fractured or because of the presence of iron oxide with the silica.

After a period of neglect, lead poisoning in young children is again receiving attention. Williams et al. (66) found the condition surprisingly common and traced the exposure to lead-bearing paints. Nothing new has been found about the biochemistry of lead poisoning, but the use of sequestering agents to aid in elimination of stored lead is receiving attention. Foreman et al. (67) have studied the successful human use of calcium-ethylenediamine-tetra-acetate for this purpose and reported that the compound is excreted unchanged in the urine within 24 hours. However, on the basis of acute tests in mice Brendel et al. (68) found no evidence that it chelates with metals in the body.

Ashe et al. (69) in animal studies found no storage of mercury and no evidence of injury upon prolonged inhalation of 1 mg. vapor per cubic meter. At higher levels both storage and injury resulted. This confirms the generally accepted hygienic standard for mercury exposure. Chronic industrial poisonings continue to be reported. Friberg (70) found in a series of workers that 0.2 to 0.3 mg. mercury per liter of urine represented an exposure that was tolerated for 10 years without effect but that higher excretion indicated exposure levels which caused tremors and more severe signs of poisoning. Locket & Nazroo (71) reported a new sign of mercury exposure, a matte brown reflection from the anterior lens capsule which varies with the time of exposure to mercury vapor, has no effect on visual acuity and occurs at concentrations which cause no other symptoms. He suggested the color as a screening test to detect past exposure to low concentrations of mercury vapor

Mancuso & Hueper (72) and Mancuso (73) have concluded on the basis of epidemiology that there is a carcinogen among workers in a plant

producing chromium. They further concluded that insoluble chromite dust and oxides of chromium may cause lung cancer by long retention in the lung. Chromium is eliminated in the urine for several years after exposure ceases.

Beryllium continues to be incompletely understood. Dutra *et al.* (74) found that beryllium oxide dust remains in the lung of the rat at least a year with little distribution to other tissues. Klemperer *et al.* (75) found in man that 0.1 mg. of beryllium inhaled in one breath can require three years for complete excretion, which supports their view that the beryllium level in the urine is not diagnostic. Spiegl *et al.* (76) suggested that exposure of humans can be evaluated by following the decrease in phospholipid to cholesterol ratio in red blood cells and the increase in uric acid to creatinine ratio in urine. Sterner & Eisenbud (77) concluded that beryllium intoxication is a modified immunological reaction with a beryllium protein complex serving as antigen.

The fluoridation of drinking water to reduce the incidence of dental caries is increasingly common. The only important recent study bearing on its safety is that of Largent (78) who showed in careful prolonged balance studies that there is fluorine storage in the human at a daily intake of 3 mg. or more but that stores are depleted at a daily intake of 0.4 to 0.8 mg. It would appear from this that the 1 p.p.m. level of fluoridation of public water supplies being used to reduce dental caries is slightly below the intake level where fluorine storage takes place. Collings *et al.* (79, 80) have carried out studies on industrial inhalation of fluorine as the acid and as rock phosphate dust. Under these conditions they find rapid elimination of the inhaled fluorine in the urine.

Chlorinated Hydrocarbons

It is unusual to be able to make direct comparisons of the effects of widely used industrial materials studied for an extended period by identical methods. For carbon tetrachloride, ethylene dichloride, trichloroethylene, and tetrachloroethylene this is made possible by a group of four papers from one laboratory: Adams *et al.* (81), Spencer *et al.* (82), Adams *et al.* (83), and Rowe *et al.* (84). Each of the vapors was administered over six-month periods to rats, guinea pigs, rabbits, and monkeys. As a result hygienic standards for human inhalation are suggested as follows: 25 p.p.m., 100 p.p.m., 200 p.p.m., and 200 p.p.m. respectively for peak concentrations during the day and about half these values for average concentrations throughout the day. These articles present clear evidence that brief peak concentrations are less tolerated than the same amount of vapor inhaled at a lower concentration over a longer period.

The most widely employed and the most frequently injurious of the chlorinated hydrocarbons is carbon tetrachloride. By means of the radiocarbon technic McCollister and associates (85) have shown that monkeys inhaling 46 p.p.m. carbon tetrachloride vapors retain 30 per cent of the vapor and eliminate it very slowly while breathing pure air. Following five

hours inhalation of 46 p.p.m., elimination through the lungs persists for at least 1800 hours, about half of the absorbed vapor leaving the body by this path. The remainder is eliminated in urine and feces, but the metabolic products could not be identified. After fifty years of toxicological study of carbon tetrachloride, its metabolism within the body remains unknown. Umiker & Pearce (86) studying 18 fatal human victims of the inhalation of carbon tetrachloride who lived more than 8 days, found pulmonary lesions consisting of fibrin exudate, a pseudomembrane lining the alveolar wall, thickening of the wall by fibroblasts, and proliferation of the epithelial lining of the alveolar walls. They showed these changes to be essentially the same as in rapidly developing uremia from renal failure and concluded that in delayed death from carbon tetrachloride the lung changes result from kidney injury, not from direct vapor injury to the lung.

LITERATURE CITED

1. Delaney, J. J., *Investigation of the Use of Chemicals in Foods and Cosmetics* (82nd Congress, 2nd Session, House of Representatives Report No. 2356, Union Calendar No. 743, Washington, D. C., 39 pp., 1952)
2. Food Protection Committee, Food and Nutrition Board, *Safe Use of Chemical Additives in Food* (National Research Council, Washington, D. C., 26 pp., 1952)
3. Fowler, R. E. L., *Agr. Food Chem.*, **1**, 469–73 (1953)
4. Oser, B. L., *Chem. Eng. News*, **29**, 2808–12 (1951)
5. Lehman, A. J., Laug, E. P., Woodard, G., Draize, J. H., Fitzhugh, O. G., and Nelson, A. A., *Food Drug Cosmetic Law Quart.*, **3**, 412–34 (1949)
6. Nale, T. W., *Ind. Med. Surg.*, **20**, 501–6 (1951)
7. Fassett, D. W., and Roudabush, R. L., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 525–29 (1952)
8. Beauvillain, A., *Arch. intern. pharmacodynamie.*, **91**, 163–75 (1952)
9. Smyth, H. F., Jr., Weil, C. S., Adams, E. M., and Hollingsworth, R. L., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 32–36 (1952)
10. McGowan, J. C., *J. Appl. Chem. (London)*, **1**(2), Suppl., S120–26 (1951)
11. McGowan, J. C., *J. Appl. Chem. (London)*, **2**, 323–28 (1952)
12. McGowan, J. C., *J. Appl. Chem. (London)*, **2**, 651–58 (1952)
13. Lehman, A. J., *Assoc. Food & Drug Officials U. S., Quart. Bull.*, **13**, 65–70 (1949)
14. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **14**, 82–98 (1950)
15. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **15**, 82–89 (1951)
16. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **15**, 122–33 (1951)
17. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **16**, 3–9 (1952)
18. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **16**, 47–53 (1952)
19. Lehman, A. J., *Assoc. Food & Drug Officials U. S. Quart. Bull.*, **16**, 85–91 (1952)
20. Lehman, A. J., *Assoc. Food & Drug Officials U. S., Quart. Bull.*, **16**, 126–32 (1952)
21. Patterson, W. I., and Lehman, A. J., *Assoc. Food & Drug Officials U. S., Quart. Bull.*, **17**, 3–12 (1953)
22. Annis, J. W., and Williams, J. W., *J. Am. Med. Assoc.*, **152**, 594–96 (1953)
23. Mountain, J. T., Zlotolow, H., and O'Connor, G. T., *Ind. Health Monthly*, **11**, 88–89 (1951)

24. Gardocki, J. F., and Hazleton, L. W., *J. Am. Pharm. Assoc., Sci. Ed.*, **50**, 491–94 (1951)
25. Lieben, J., Waldman, R. K., and Krause, L., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 491–95 (1952)
26. Lieben, J., Waldman, R. K., and Krause, L., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 93–98 (1953)
27. Barnes, J. M., and Denz, F. A., *J. Hyg.*, **49**, 430–41 (1951)
28. Holland, E. G., Hazleton, L. W., and Hanzal, D. L., *Federation Proc.*, **11**, 357 (1952)
29. Ingle, L., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 357–67 (1952)
30. Ambrose, A. M., Christensen, H. E., Robbins, D. J., and Rather, L. J., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 197–210 (1953)
31. Davidow, B., and Frawley, J. P., *Proc. Soc. Exptl. Biol. Med.*, **76**, 780–83 (1951)
32. Davidow, B., and Radomski, J. L., *J. Pharmacol. Exptl. Therap.*, **107**, 259–65 (1953)
33. Radomski, J. L., and Davidow, B., *J. Pharmacol. Exptl. Therap.*, **107**, 266–72 (1953)
34. Spencer, J. N., *Federation Proc.*, **12**, 368 (1953)
35. Hodge, H. C., Maynard, E. A., and Blanchet, H. J., Jr., *J. Pharmacol. Exptl. Therap.*, **104**, 60–66 (1952)
36. Drill, V. A., and Hiratzka, T., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 61–67 (1953)
37. Harrisson, J. W. E., Ambrus, J. L., Ambrus, C. M., Rees, E. W., Peters, R. H., Jr., Reese, L. C., and Baker, T., *J. Am. Med. Assoc.*, **149**, 1520–22 (1952)
38. Lindenbaum, A., White, M. R., and Schubert, J., *J. Biol. Chem.*, **190**, 585–93 (1951)
39. Peters, R. A., Wakelin, R. W., and Buffa, P., *Proc. Roy. Soc. (London)*, [B]**140**, 497–506 (1953)
40. Chenoweth, M. B., Kandel, A., Johnson, L. B., Bennett, D. R., Scott, E. B., and Seki, S. L., *J. Pharmacol. Exptl. Therap.*, **102**, 31–49 (1951)
41. Parker, V. H., Barnes, J. M., and Denz, F. A., *Brit. J. Ind. Med.*, **8**, 226–35 (1951)
42. Harvey, D. G., Bidstrup, P. L., and Bonnell, J. A. L., *Brit. Med. J.*, **II**, 13–16 (1951)
43. Pollard, A. B., and Filbee, J. F., *Lancet*, **II**, 618–19 (1951)
44. Culver, P. C., Wilcox, C. S., Jones, C. M., and Rose, R. S., Jr., *J. Pharmacol. Exptl. Therap.*, **103**, 377–81 (1951)
45. Harris, R. S., Sherman, H., and Jetter, W. M., *Arch. Biochem. and Biophysics*, **34**, 249–58 (1951)
46. Harris, R. S., Sherman, H., and Jetter, W. M., *Arch. Biochem. and Biophysics*, **34**, 259–65 (1951)
47. Reiser, R., Bryson, M. J., Carr, M. J., and Kuiken, K. A., *J. Biol. Chem.*, **194**, 131–38 (1952)
48. Hine, C. H., Anderson, H. H., Moon, H. D., Dunlap, M. K., and Morse, M. S., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 282–91 (1953)
49. Fitzhugh, O. G., Nelson, A. A., and Frawley, J. P., *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 583–86 (1951)
50. Smith, C. C., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 310–18 (1953)

51. Devel, H. L., Jr., Greenberg, S. M., Calbert, C. E., Baker, R., and Fisher, M. R., *Food Research*, **16**, 258–80 (1951)
52. Sikes, D., and Bridges, M. E., *Science*, **116**, 506–7 (1952)
53. Bell, W. B., *Virginia J. Science*, **3**, 169–77 (1952)
54. Bell, W. B., *Vet. Med.*, **48**, 135–40, 146 (1953)
55. Hansel, W., McEntee, K., and Olafson, P., *Cornell Vet.*, **41**, 367–76 (1951)
56. McEntee, K., and Olafson, P., *Fertility & Sterility*, **4**, 128–36 (1953)
57. Cadle, R. D., and Magill, P. L., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 74–84 (1951)
58. Amdur, M. O., Schulz, R. Z., and Drinker, P., *Arch. Ind. Hyg. and Occupational Med.*, **5**, 318–29 (1952)
59. Amdur, M. O., Silverman, L., and Drinker, P., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 305–13 (1952)
60. Gray, E. LeB., MacNamee, J. K., and Goldberg, S. B., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 20–21 (1952)
61. Vintinner, F. J., and Baetjer, A. M., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 206–16 (1951)
62. Clelland, D. W., Cumming, W. W., and Ritchie, P. D., *J. Appl. Chem. (London)*, **2**, 31–41 (1952)
63. Clelland, D. W., Cumming, W. W., and Ritchie, P. D., *J. Appl. Chem. (London)*, **2**, 42–48 (1952)
64. King, E. J., Mohanty, G. P., Harrison, C. V., and Nagelschmidt, G., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 455–77 (1953)
65. Policard, A., and Collet, A., *Arch. Ind. Hyg. and Occupational Med.*, **5**, 527–34 (1952)
66. Williams, H., Kaplan, E., Couchman, C. E., and Sayers, R. R., *Public Health Repts. (U. S.)*, **67**, 230–36 (1952)
67. Foreman, H., Hardy, H. L., Shipman, T. L., and Belknap, E. L., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 148–51 (1953)
68. Brendel, R., Swayne, V., Preston, R., Beiler, J. M., and Martin, G. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 123–24 (1953)
69. Ashe, W. F., Largent, E. J., Dutra, F. R., Hubbard, D. M., and Blackstone, M., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 19–43 (1953)
70. Friberg, L., *Nord. Hyg. Tidskr.*, **32**, 240 (1951)
71. Locket, S., and Nazroo, I. A., *Lancet*, **I**, 528–30 (1952)
72. Mancusco, T. F., and Hueper, W. C., *Ind. Med. and Surg.*, **20**, 358–63 (1951)
73. Mancusco, T. F., *Ind. Med. and Surg.*, **20**, 393–407 (1951)
74. Dutra, F. R., Largent, E. J., Cholak, J., Hubbard, D. M., and Roth, J. L., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 65–73 (1951)
75. Klemperer, F. W., Martin, A. P., and Van Riper, J., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 251–56 (1951)
76. Spiegl, C. J., LaFrance, L., and Ashworth, B. J., *Arch. Ind. Hyg. and Occupational Med.*, **7**, 319–25 (1953)
77. Sterner, J. H., and Eisenbud, M., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 123–51 (1952)
78. Largent, E. J., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 37–42 (1952)
79. Collings, G. H., Jr., Fleming, R. B. L., and May R., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 585–90 (1951)

80. Collings, G. H., Jr., Fleming, R. B. L., May R., and Bianconi, W. O., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 368–73 (1952)
81. Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., and Irish, D. D., *Arch. Ind. Hyg. and Occupational Med.*, **6**, 50–66 (1952)
82. Spencer, H. C., Rowe, V. K., Adams, E. M., McCollister, D. D., and Irish, D. D., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 482–93 (1951)
83. Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., and Irish, D. D., *Arch. Ind. Hyg. and Occupational Med.*, **4**, 469–81 (1951)
84. Rowe, V. K., McCollister, D. D., Spencer, H. C., Adams, E. M., and Irish, D. D., *Arch. Ind. Hyg. and Occupational Med.*, **5**, 566–79 (1952)
85. McCollister, D. D., Beamer, W. H., Atchison, G. J., and Spencer, H. C., *J. Pharmacol. Exptl. Therap.*, **102**, 112–24 (1951)
86. Umiker, W., and Pearce, J., *Arch. Pathol.*, **55**, 203–17 (1953)

DERMATOLOGY[1]

By Donald M. Pillsbury and Walter B. Shelley

School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

During the past two years, several significant advances in the treatment of various diseases affecting the skin have been made. To some extent, the effectiveness of newer methods of treatment has increased the understanding of the basic etiologic factors in the diseases treated, and has served as a stimulus for new investigational approaches. This review will be concerned partially with an attempt at critical interpretation of several new therapeutic methods which have apparently achieved some usefulness. In addition, two other dermatologic syndromes will be considered in respect to advances which have been made in a better understanding of the etiologic factors involved, namely diseases related to disturbances in the sweat gland, and urticaria pigmentosa.

Steroid therapy, especially cortisone and corticotropin, has brought about a major upheaval in the treatment of diseases of the skin. The immediate short term results of such therapy upon the course of a wide variety of diseases affecting the skin are undoubted and spectacular. In the treatment of severe acute self-limited processes in which steroid therapy is required for short periods of time, it would appear that steroid therapy is firmly established as an effective and justifiable method of treatment. In a wide variety of chronic diseases affecting the skin, however, it has become clearly apparent that the doses of cortisone and corticotropin required to keep the disease under control are so high, and the risks of the attendant general physiologic effects so serious, as to make such therapy far less justifiable. It seems quite clear that discussion of this problem will continue for several years, and that probably the true usefulness of steroid therapy, in terms of benefit to the patient as a whole, will not be determined with some diseases of the skin until many more long-term studies are available. There is reason to believe, however, on the basis of continued observation of many dermatologic patients in whom steroid therapy has been injudiciously administered, that occasional deaths in the treatment of some unimportant and relatively benign dermatoses will be brought about. This is a matter for most careful and critical inquiry.

Data on the effectiveness of topical hydrocortisone therapy are as yet quite conflicting, except to indicate that such treatment is apparently without significant risk. Our summary of this method of treatment will necessarily be incomplete, and probably outdated by the time this review is published. Nevertheless, certain facts seem evident from the scattered published re-

[1] The survey of literature pertaining to this review was completed in November, 1953.

ports on this method of treatment, and from our own fairly extensive experience.

A surprising and unsuspected advance in therapy has occurred in the use of antimalarial compounds in the treatment of chronic discoid lupus erythematosus and polymorphic eruptions attributed to photosensitivity. The long-term effects of such therapy, particularly in regard to the cumulative incidence of reactions with repeated courses of treatment, are as yet unknown. Nevertheless, the short-term effects in some patients have been undeniable and striking, and will be reviewed in some detail.

Fungous infections of man, sometimes superficial and banal, but occasionally systemic and productive of a high mortality, have long remained a common group of infectious diseases for which there is no satisfactory treatment. The therapy of fungous infections is presently at about the same state as that of bacterial infections prior to the introduction of sulfonamides. Nevertheless, compounds having antifungal effects are regularly becoming available, and a few of these have shown modest promise in clinical application.

CORTISONE, HYDROCORTISONE, AND CORTICOTROPIN THERAPY IN SKIN DISEASES

Experimental and theoretical considerations.—The precise mechanism of action of the adrenal corticoids at the cellular level remains unknown. The skin, being an organ which can be observed directly, and from which tissue can be removed without risk to the patient, is an excellent site at which to observe the changes produced by the adrenal corticoids. The available data upon the mechanisms of action of such treatment on the skin have recently been summarized by Pillsbury & Urbach (1).

The adrenal corticoids are of most immediate practical value in the treatment of those dermatoses proven or suspected of being of allergic origin. Study of the alterations in allergic mechanisms produced by steroid therapy has so far led to the conclusion that there is no clinically significant reduction in antibody formation, and no demonstrable action on the union of antigen and antibody. The beneficial effect seems to take place at the cellular level, perhaps by alteration of cell membrane permeability or by interference with the action of whatever noxious agent is produced by antigen-antibody union (2).

The immediate cutaneous wheal-type allergic reaction, presumably mediated by thermolabile reagin is not affected by administration of the C_{11} oxygenated steroids (3). The delayed granulomatous skin response attributable to sessile (cellular) antibodies is frequently depressed, although not completely inhibited (4). Patch tests in patients with contact dermatitis also are not affected, except in a very narrow range with high dilutions (5). As might be expected from the observation that adrenal corticoids reduce vascular damage but do not interfere with circulating antibody, it would appear that the Shwartzman phenomenon is inhibited by these compounds (6). The development of the Arthus reaction, which is an expression of hypersensitiv-

ity mediated by circulating reagin, is not affected (7). The conclusion that the adrenal cortical hormones act at the cellular level is entirely compatible with the observation that their beneficial effects are attributable to suppression of the symptoms, but not to any effect on the underlying allergic disease.

Cortisone and hydrocortisone are absorbed through the mucous membranes of animals and humans and through the very thin skin of small experimental animals such as the mouse (8). Their anti-inflammatory effects may be readily demonstrated in man on the conjunctiva and the nasal mucosa. Unfortunately, the results of the topical application of cortisone to human skin have been disappointing clinically, and this may be a result in part of the very small amount of the compound which is absorbed through the skin to the site of the inflammatory reaction. Hydrocortisone, on the other hand, has much more definite clinical effects on inflamed skin, though they are extremely variable, for reasons for which are not yet well understood. In the mouse, topically applied cortisone causes thinning of the epidermis, cessation of hair growth, and decrease in the size of the sebaceous glands. The thickness of the skin is reduced, apparently because of loss of substance from the collagenous fibers. This effect is temporary, and the mouse skin eventually becomes refractory to the local application of cortisone if it is continued long enough. Intradermal administration of cortisone and hydrocortsone in doses too small to cause systemic effects results in decrease of cutaneous reactivity to delayed-type allergic responses such as reactions to insect bites (9).

Knowledge of the action of the adrenal steroids on the connective tissue is of importance in understanding the beneficial effects of these compounds on syndromes such as the collagen diseases and pemphigus. They may act by:

(a) Suppressing osmosis through semipermeable membranes.

(b) Decreasing permeability of capillaries (probably indirectly).

(c) Decreasing the spreading effect of hyaluronidase (probably by acting on the hyaluronate substrate).

(d) Reducing the number of fibroblasts and the production of collagen fibers (perhaps through interference with the synthesis of chondroitin sulfuric acid).

(e) Exerting a catabolic action on proteins, eventually resulting in reduction of antibody titres, by interference with gamma globulin synthesis (10).

CLINICAL EFFECTS OF CORTISONE AND CORTICOTROPIN ON DISEASES AFFECTING THE SKIN

The decision as to whether or not adrenal corticoid therapy should be employed in a particular patient is dependent upon whether or not the risks of such therapy are justified by the morbidity or mortality of the disease being treated. It is convenient to consider the effects of such treatment in respect to the following classes of diseases in which the skin is involved:

(I) Diseases of serious medical import in which the skin is frequently or

ports on this method of treatment, and from our own fairly extensive experience.

A surprising and unsuspected advance in therapy has occurred in the use of antimalarial compounds in the treatment of chronic discoid lupus erythematosus and polymorphic eruptions attributed to photosensitivity. The long-term effects of such therapy, particularly in regard to the cumulative incidence of reactions with repeated courses of treatment, are as yet unknown. Nevertheless, the short-term effects in some patients have been undeniable and striking, and will be reviewed in some detail.

Fungous infections of man, sometimes superficial and banal, but occasionally systemic and productive of a high mortality, have long remained a common group of infectious diseases for which there is no satisfactory treatment. The therapy of fungous infections is presently at about the same state as that of bacterial infections prior to the introduction of sulfonamides. Nevertheless, compounds having antifungal effects are regularly becoming available, and a few of these have shown modest promise in clinical application.

CORTISONE, HYDROCORTISONE, AND CORTICOTROPIN THERAPY IN SKIN DISEASES

Experimental and theoretical considerations.—The precise mechanism of action of the adrenal corticoids at the cellular level remains unknown. The skin, being an organ which can be observed directly, and from which tissue can be removed without risk to the patient, is an excellent site at which to observe the changes produced by the adrenal corticoids. The available data upon the mechanisms of action of such treatment on the skin have recently been summarized by Pillsbury & Urbach (1).

The adrenal corticoids are of most immediate practical value in the treatment of those dermatoses proven or suspected of being of allergic origin. Study of the alterations in allergic mechanisms produced by steroid therapy has so far led to the conclusion that there is no clinically significant reduction in antibody formation, and no demonstrable action on the union of antigen and antibody. The beneficial effect seems to take place at the cellular level, perhaps by alteration of cell membrane permeability or by interference with the action of whatever noxious agent is produced by antigen-antibody union (2).

The immediate cutaneous wheal-type allergic reaction, presumably mediated by thermolabile reagin is not affected by administration of the C_{11} oxygenated steroids (3). The delayed granulomatous skin response attributable to sessile (cellular) antibodies is frequently depressed, although not completely inhibited (4). Patch tests in patients with contact dermatitis also are not affected, except in a very narrow range with high dilutions (5). As might be expected from the observation that adrenal corticoids reduce vascular damage but do not interfere with circulating antibody, it would appear that the Shwartzman phenomenon is inhibited by these compounds (6). The development of the Arthus reaction, which is an expression of hypersensitiv-

ity mediated by circulating reagin, is not affected (7). The conclusion that the adrenal cortical hormones act at the cellular level is entirely compatible with the observation that their beneficial effects are attributable to suppression of the symptoms, but not to any effect on the underlying allergic disease.

Cortisone and hydrocortisone are absorbed through the mucous membranes of animals and humans and through the very thin skin of small experimental animals such as the mouse (8). Their anti-inflammatory effects may be readily demonstrated in man on the conjunctiva and the nasal mucosa. Unfortunately, the results of the topical application of cortisone to human skin have been disappointing clinically, and this may be a result in part of the very small amount of the compound which is absorbed through the skin to the site of the inflammatory reaction. Hydrocortisone, on the other hand, has much more definite clinical effects on inflamed skin, though they are extremely variable, for reasons for which are not yet well understood. In the mouse, topically applied cortisone causes thinning of the epidermis, cessation of hair growth, and decrease in the size of the sebaceous glands. The thickness of the skin is reduced, apparently because of loss of substance from the collagenous fibers. This effect is temporary, and the mouse skin eventually becomes refractory to the local application of cortisone if it is continued long enough. Intradermal administration of cortisone and hydrocortsone in doses too small to cause systemic effects results in decrease of cutaneous reactivity to delayed-type allergic responses such as reactions to insect bites (9).

Knowledge of the action of the adrenal steroids on the connective tissue is of importance in understanding the beneficial effects of these compounds on syndromes such as the collagen diseases and pemphigus. They may act by:

(a) Suppressing osmosis through semipermeable membranes.

(b) Decreasing permeability of capillaries (probably indirectly).

(c) Decreasing the spreading effect of hyaluronidase (probably by acting on the hyaluronate substrate).

(d) Reducing the number of fibroblasts and the production of collagen fibers (perhaps through interference with the synthesis of chondroitin sulfuric acid).

(e) Exerting a catabolic action on proteins, eventually resulting in reduction of antibody titres, by interference with gamma globulin synthesis (10).

CLINICAL EFFECTS OF CORTISONE AND CORTICOTROPIN ON DISEASES AFFECTING THE SKIN

The decision as to whether or not adrenal corticoid therapy should be employed in a particular patient is dependent upon whether or not the risks of such therapy are justified by the morbidity or mortality of the disease being treated. It is convenient to consider the effects of such treatment in respect to the following classes of diseases in which the skin is involved:

(I) Diseases of serious medical import in which the skin is frequently or

always affected, and in which cortisone and corticotropin are useful in varying degrees.

(II) Nonfatal skin diseases capable of producing prolonged partial or complete disability.

(III) Acute, relatively self-limited, diseases affecting the skin, in which the symptoms and disability may be mild to extreme.

(IV) Other diseases of various types in which cortisone or corticotropin are rarely indicated, or may actually have a harmful effect on the disease in question.

I. The principal medical diseases of serious general medical import in which the skin is affected, and in which steroid therapy has found some usefulness, are the collagen diseases, pemphigus, and variants of erythema multiforme.

The collagen diseases are systemic affections, in which cutaneous signs are incidental and frequently absent. This discussion will be confined to that member of the collagen group, acute disseminated lupus erythematosus, in which cutaneous lesions are most frequently found. Reports on the effects of cortico-steroid therapy in the treatment of acute disseminated lupus erythematosus are numerous (11 to 18).

The effectiveness of cortisone and corticotropin in controlling acute crises of disseminate lupus erythematosus has been demonstrated without doubt. Enormous doses, as much as 500 to 1000 mg. of cortisone daily, may be necessary in some patients. It seems quite certain that a considerable percentage of these patients with severe acute exacerbations of lupus erythematosus would not have survived without adrenal cortical therapy. In this sense, such treatment may be regarded as lifesaving. On the other hand, there is unfortunately no indication that cortisone and corticotropin therapy have a significant effect in staying the relentless progress of this extraordinarily chronic disease. In patients to whom it has been found necessary to administer cortisone or corticotropin to control an acute exacerbation, continuance of such therapy in reduced dosage is ordinarily necessary.

Careful painstaking histories in patients with disseminate visceral lupus erythematosus will frequently yield suggestive findings extending back to many years. The disease is one of extreme chronicity. Of particular interest is the fact that a persistent biologic false-positive test for syphilis may be an early sign of diffuse collagen disease (19, 20).

It is indeed a remarkable commentary upon progress in medicine to note that less than ten years ago a specific positive test for syphilis was grave evidence of a disease in which a cure was doubtful and the prognosis uncertain. In contrast, at present, because cure of early syphilis and the prevention of late sequelae can be assured with almost absolute certainty, such a specific positive test is no great cause for alarm. Some ten years ago, evidence began to accumulate rapidly regarding the frequency of biologic false-positive reactions of short duration following a wide variety of infections, (upper re-

spiratory infection, pneumonia, vaccination takes, infectious mononucleosis, etc.), and the occurrence of false-positive tests in association with more chronic diseases such as malaria and leprosy. Such a finding was, however, regarded as incidental, and of no significance other than making it necessary to determine that the patient did not have syphilis. It is now clear that the patient who has a specific positive test for syphilis is relatively fortunate, while in patients who show a "persistent" or "recurrent" biologic false-positive test, the possibility of a diffuse collagen disease is considerable.

The probability that cortisone therapy may do no more in acute disseminate lupus erythematosus than control acute exacerbations and suppress their recurrence without influencing the basic pathologic process, reemphasizes the importance of other factors in the management of this disease. Patients with disseminate lupus are frequently in a state of extremely precarious balance between reasonable health and extreme ill health. We have observed the apparent exacerbation of disseminate lupus from a subacute to an acute state by any one of the following forms of trauma: (a) exposure to sunlight (frequent); (b) injection of a gold compound; (c) attempted removal of a focus of infection; (d) ureteral catherization in pyelitis; (e) work involving repeated physical trauma to the skin and subcutaneous tissues; (f) administration of sensitizing drugs, such as sulfonamides or penicillin; (g) intercurrent infection; (h) injection of a considerable variety of bacterial antigens, including tuberculin and autogenous vaccines. It would seem as if a patient with subacute disseminate lupus erythematosus is in a state whereby the production of a wide variety of local or general disturbances may induce a chain reaction in the vascular tree, resulting in a fullblown exacerbation. Avoidance of such trauma is of the greatest importance in the management of a patient with lupus erythematosus, and complete reliance must not be placed in the suppressive effects of adrenal cortical therapy.

Bullous eruptions of the skin and mucous membranes.—Bullous lesions of the skin may occur as a result of physical trauma, such as burns, or as part of a sensitization reaction to external contactants. Under such circumstances, the cause of the reaction is ordinarily apparent. In addition, there is a group of diseases which are characterized by a slow or rapid onset of bullous lesions involving small to large areas of skin and mucous membranes, by frequent superficial or systemic secondary bacterial infection, and often by progressive debilitation. Three major groups of such diseases have been recognized: (a) pemphigus; (b) dermatitis herpetiformis; and (c) erthema multiforme-like eruptions. The etiologic factors involved in the first two diseases are entirely unknown; in erythema multiforme, the onset of the eruption may sometimes be traced to various agents such as drugs, viral and bacterial infections, "toxic" reactions in association with neoplasms, irradiation, and allergic reactions. It is important that such a reaction be classified as rapidly as possible, because the treatment and eventual prognosis vary considerably. The

methods of arriving at a correct diagnosis, principally on the basis of biopsies and smears, have been rendered more accurate and rapid in recent years.

Pemphigus.—Pemphigus is a characteristic bullous disease of the skin and mucous membranes, of extreme chronicity and, until cortisone and corticotropin became available, always fatal within months or a few years. During the initial phase of the disease only minor discomfort and disability result, and an accurate diagnosis is frequently not made. It is our belief that it is extremely important to recognize the disease at this time, however, because treatment with cortisone or corticotropin may bring the process under control with relatively low doses of the compounds, while the patient is still in a state of excellent general health. A delay in making the diagnosis may increase the problem of treatment enormously, and introduce factors of infection and of severe disturbance of the nutritional status which are not controllable by relatively simple therapy.

An excellent monographic article on pemphigus has recently been published by Lever (21). This paper is well worth reading in the original. Briefly, pemphigus is characterized by the following:

(*a*) Large flaccid bullae develop on normal or slightly erthematous skin with resultant denudation and granulating erosion. Initial lesions may be entirely confined to the mucous membranes of the mouth and vagina.

(*b*) The first lesions ordinarily occur around body orifices, on pressure sites, or on intertriginous areas. Initially the process may show mild exacerbation and spontaneous remissions, but it ordinarily becomes steadily progressive, with increasing extent of involvement. At this time no related visceral disease is demonstrable as a rule.

(*c*) After the muco-cutaneous involvement becomes extensive, rapid debilitation may occur, with marked hypoproteinemia, anemia, cachexia resulting from dysphagia and protein loss, and serious systemic secondary infection. True pemphigus, untreated, is almost uniformly fatal in periods varying from a few months to several years.

(*d*) Acantholysis is a characteristic histological feature of the lesions, and may be demonstrated by a simple diagnostic technique (22). This is called the Tzanck test and consists of examination of Giemsa stained scrapings from the base or edge of a fresh bulla. In pemphigus, the smears show large sheaths and clusters of rounded epithelial cells which have lost their prickles, have a relatively large oval nucleus, and show condensation of the cytoplasmic nuclear protein around the periphery of the cell. This gives the appearance of a bluish halo about the cell margin, separated by a lighter staining protoplasmic ring from the nucleus. The phenomenon is almost always demonstrable in smears taken from "early" pemphigus bullae, and is quite diagnostic since it reflects the basic change of acantholysis. The characteristics are also, of course, clearly demonstrable in biopsies, provided an old lesion is not selected.

Our own experience in the treatment of pemphigus with cortisone and corticotropin entirely confirms that of Lever, and of the other observers

whose work he has summarized. As mentioned above, the problem of treatment becomes enormously complicated if it is delayed until extensive involvement of the mucous membranes and skin has occurred. It is believed that pemphigus is one of the few chronic diseases in which steroid therapy is justified as soon as a diagnosis is made, because it is invariably progressive, and evidence of the disease may often be suppressed with small, relatively safe, doses of cortisone or ACTH (adrenocoticotropin) if the extension of the disease has been minimal. Later, very serious treatment risks must often be assumed. It will frequently be found that the amount of cortisone required may be so great in more advanced cases as to make ACTH the preferable method of treatment. We are currently following a number of patients with pemphigus in whom all evidence of the disease can be suppressed by ACTH therapy in doses of the order of 20 to 40 units every fifth or sixth day. It is obvious that such prolonged treatment necessitates most careful observation of the patient for evidence of undesirable physiologic effects, but in the treatment of pemphigus, the risks of such treatment are well worth taking.

Erythema multiforme-like bullous eruptions.—This group of diseases shows wide variability in symptoms and clinical signs. In some patients, a mild eruption may be recurrent, often seasonally, for many years. The more common and severe types, however, are generally characterized by the following:

(*a*) The onset is usually rapid. Widespread cutaneous involvement occurs, with tense often large bullae arising from erythematous or urticarial skin. The erosions are ordinarily small, do not spread by extension, and heal rapidly unless secondary infection is present. Fever is common.

(*b*) The disease is ordinarily acute, and lasts for a few weeks as a rule. Spontaneous remission usually occurs. In very occasional instances, recurrences are traceable to the readministration of a drug, but more often the exact precipitating factor remains unknown.

(*c*) The syndrome is more common in younger age groups, and may occur in children (Stevens-Johnson type). The mortality is low.

The eruption may be differentiated from pemphigus quite easily as a rule by the clinical findings and by the absence of acantholytic epidermal cells in smears. These ordinarily show many polymorphonuclear and eosinophilic white blood cells, along with much fibrin debris.

Reports on the use of cortisone and ACTH in the erythema multiforme group of diseases are few (11, 17, 23). These reports, coupled with our own experience in some eight patients, would indicate that cortisone or ACTH therapy is indicated in any patient with severe erythema multiforme reactions, in the absence of any overriding contraindication. It is almost invariably helpful to some degree, though the lesions may require two to three weeks to disappear completely. Whether or not such therapy will suffice to prevent the progressive ocular change of essential shriveling of the conjunctiva seen occasionally after erythema multiforme is not yet established.

Dermatitis herpetiformis.—Cortisone and ACTH therapy have rarely proven to be effective in this disease and, if so, only temporarily.

II. Nonfatal skin diseases capable of producing prolonged slight to complete disability. Of this large group of diseases, only a few in which some experience with steroid therapy has been acquired will receive comment.

The addition of steroid therapy has not greatly changed the outlook in psoriasis. In the generalized exfoliative phases of the disease, particularly in patients with associated rheumatoid arthritis, such therapy may at times be helpful, and is worthy of trial. In the chronic typical forms of the disease, all observers are agreed that cortisone and corticotropin therapy is rarely helpful, and at best has very fleeting effects. Such treatment is definitely not advised. This is most unfortunate, because, while there are many treatments for psoriasis, none of them is more than temporarily effective. The basic etiologic factors of the disease remain a complete mystery, and we are unaware of any serious investigation of it on a broad integrated scale.

The chief chronic nonfatal skin diseases in which information on adrenocortical therapy is available are various types of dermatitis and eczema. In certain of these, the experience has been sufficient to come to some tentative conclusion as to the probable place of such treatment in their management. One conclusion seems inescapable, namely that cortisone and ACTH are being used in more or less trivial manifestations of these diseases at times, and that assumption of the inherent physiologic risks of such therapy cannot be justified on the basis of the inherent risks, or even discomfort, of the disease being treated. It must be kept in mind that once treatment is started in some types of eczema, the problem of withdrawal of cortisone therapy becomes one of great difficulty.

Patients with various forms of dermatitis represent at least 50 per cent of all individuals presenting themselves for treatment of a disease affecting the skin, in our experience. Unfortunately, a rather bewildering array of terms has been applied to various types of dermatitis, and this renders a discussion of treatment of them difficult. However, there has been some recent indication of a trend toward simplification of terminology, and agreement upon the principal types of dermatitis composing this important group of skin diseases. The following classification has recently been suggested by one of us (24): (a) Acute contact dermatitis; (b) Atopic dermatitis; (c) Seborrheic dermatitis; (d) Eczematous contact-type dermatitis; (e) Nummular dermatitis; (f) Lichen simplex chronicus (circumscribed neurodermatitis); (g) Chronic dermatitis of hands and/or feet; (h) Stasis dermatitis; (i) Miscellaneous dermatitis (including dermatitis directly or indirectly related to internal medical diseases, obscure erythrodermas, lymphoblastomas, etc.).

The treatment of acute contact dermatitis with cortisone and ACTH will be discussed briefly below. In certain types of dermatitis, such therapy is rarely or almost never justifiable, e.g., lichen simplex chronicus, stasis dermatitis, mild to moderate seborrheic dermatitis. The greatest experience with steroid therapy has been achieved in atopic dermatitis (11, 17, 25). The experience with this type of dermatitis is, in general, applicable to other forms of extensive chronic dermatitis in which cortisone therapy may at

times seem justified, e.g., extensive seborrheic dermatitis, nummular dermatitis, extensive eczematous contact-type dermatitis.

In a significant percentage of patients, probably about 25 per cent, the results of cortisone or corticotropin therapy in atopic dermatitis will be disappointing, the improvement varying from none to moderate. This is ordinarily the case when the inflammatory changes in the skin are less acute, in those patients in whom the skin is very dry, and in whom the objective changes are produced almost entirely by scratching. Under such circumstances this failure in treatment will soon be apparent in most patients within three or four days after cortisone therapy is started. When this is definitely established, it is of the greatest importance to discontinue cortisone therapy promptly, and not to continue it futilely for two to three weeks.

In very acute severe flareups of atopic dermatitis, with marked inflammatory changes in the skin, the initial effect of cortisone therapy is ordinarily excellent. In respect to further progress, such patients fall into one of three general groups:

(a) Patients in whom the improved state of the skin is maintained consistently as the dose is reduced over a period of three or four weeks, and who do not experience any significant "rebound" of the dermatitis after complete withdrawal of cortisone therapy, gradually achieved. This is an ideal response to cortisone therapy, but unfortunately, it is observed in a "very small" group of patients, certainly not over 10 per cent.

(b) In another group, probably the largest, gradual reduction of the dose of cortisone will reveal a critical level required to keep the eczema under reasonable control. Fortunately, this dose is often one which does not usually present serious physiologic risk, i.e., 25 to 75 mg. daily. Nevertheless, every effort should be made to find a means of discontinuing cortisone entirely, including various types of local therapy, psychotherapy in selected cases, and trial of a change in environment if possible. Occasionally, administration of a short course of corticotropin is helpful in accomplishing complete withdrawal of cortisone.

(c) In a considerable group of patients, probably between 10 and 25 per cent it will be found that the "critical" dose of cortisone is of the order of 100 to 200 mg. per day. This presents a difficult problem. Such patients are extremely unwilling to accept a recurrence of the eczema, and may even obtain cortisone on their own responsibility.

Certain general rules seem clear on the basis of the experience with cortisone and corticotropin therapy in chronic dermatitis to date. One may adopt the attitude of never administering such treatment for chronic dermatitis regardless of its severity, but most physicians will be unwilling to adhere to this. Assuredly, however, less hazardous methods of management should be given a very thorough and painstaking trial before resorting to steroid therapy. The dermatitis or eczema to be treated must be severe, extensive, and disabling, not just annoying. The critical level of dosage should be ascertained as rapidly as possible, and "maintenance" therapy continued

just below this as a rule, in order that spontaneous changes in the course of the dermatitis may be apparent, and the effectiveness of other methods of treatment determined.

III. Acute relatively self-limited diseases affecting the skin.

The principal examples of this group of diseases affecting the skin are contact dermatitis, i.e., an epidermal sensitization reaction to a plant or some chemical substance, and acute allergic reactions to drugs administered internally. In both of these reactions, cortisone and ACTH therapy are almost invariably effective, and the risk of such therapy is small because the duration of treatment necessary is short, no more than three or four days (26, 27)

Unfortunately, it is clear that adrenocortical therapy is being applied with considerable abandon in the treatment of mild contact dermatitis. It is our own practice to restrict such treatment to patients with severe and extensive eruptions. The evidence is clear that if continued exposure to the allergen is occurring during cortisone or corticotropin therapy, a reaction in the skin will not be prevented, and we have observed several patients who sustained relapses of contact dermatitis on re-exposure while taking moderate to large doses of cortisone. Patch test reactions are not significantly interfered with by the administration of 150 mg. of cortisone daily. Sulzberger *et al.* (28) showed that there is a small but consistent trend toward diminution of the reaction of the sites of application of "threshold" concentrations of the allergen, but in the case of concentrations capable of producing fully developed strong reactions, no inhibition of the inflammatory response was produced.

This brief discussion of the effects of cortisone and ACTH on diseases in which the skin is affected primarily or incidentally may be summarized as follows (1):

TABLE I

CORTISONE AND CORTICOTROPIN IN DISEASES OF THE SKIN*

Disease Syndrome	Effectiveness of Cortisone/Corticotropin Therapy	Justification for Clinical Use
Angioneurotic edema	Very effective.	If severe, particularly if there is risk of laryngeal involvement.
Contact dermatitis	Very effective.	Internal cortisone therapy justified only in very severe and extensive involvement.
Dermatitis medicamentosa	Effectiveness varies depending on type of eruption.	Fully justified in severe cases, particularly if internal organs, as well as the skin, are shock sites of the reaction.

* From Pillsbury, D. M., and Urbach, F., in *Medical Uses of Cortisone* (The Blakiston Co., Inc., New York, N. Y., in press).

TABLE I—*Continued*

Disease Syndrome	Effectiveness of Cortisone/Corticotropin Therapy	Justification for Clinical Use
Atopic dermatitis	Variable, but "morbidistatic" in probably 75 per cent of cases.	"Only" in carefully selected patients with extensive disabling involvement. Prolonged therapy often necessary. "Not" to be used in mild to moderate forms.
Exfoliative dermatitis	Variable, particularly effective in allergic dermatitis.	Almost always indicated in severe extensive involvement, though necessary therapy may be prolonged.
Seborrheic dermatitis	Highly effective.	Careful consideration necessary. Justified only in severe extensive involvement not controlled by other methods of treatment. Hydrocortisone ointment may be preferable in some patients.
Pemphigus	Regularly effective, though very high doses usually necessary.	Always justified and indicated unless some very compelling contraindication to steroid therapy exists.
Polyarteritis nodosa	Temporarily effective.	Ordinarily indicated.
Thrombocytopenic purpura	Variably effective.	Variable; always if severe.
Nummular dermatitis	Almost always effective.	Variable; usually not justified. Reserve for extensive severe involvement, with realization that prolonged therapy or repeated courses may be necessary.
Erythema multiforme (all types)	Only effective method of treatment.	Justified in severe cases, provided no contraindication. Occasionally, though not commonly, prolonged therapy necessary.
"Id" eruptions	Almost always effective.	Severe cases only.
Erythema nodosum	Almost always.	Variable, depending on severity. Careful study to determine whether lesions are part of invasive phase of infection, such as tuberculosis or coccidioidomycosis. Great caution advisable.
Visceral lupus erythematosus (acute disseminated lupus erythematosus)	Almost always morbidostatic, but high doses and very prolonged therapy frequently necessary.	For control of acute exacerbations; probably not advisable in low-grade manifestations of the disease.

TABLE I—*Continued*

Disease Syndrome	Effectiveness of Cortisone/Corticotropin Therapy	Justification for Clinical Use
Cutaneous lupus erythematosus (chronic discoid)	Uncertain and variable.	Not recommended. Chloroquin or atabrin effective. Gold salts "not" recommended.
Psoriasis	Only occasionally effective, particularly in extensive involvement of skin with arthritis.	Only severe cases. Not indicated in ordinary chronic psoriasis.
Sarcoidosis	Variable and uncertain.	Rarely to sometimes by no means always.
Mycosis fungoides	Extremely variable; other methods, such as x-ray, have more regular effect.	Rarely.
Chronic anal and vulvar pruritus	Internal administration variably effective. Hydrocortisone ointment apparently superior, often strikingly so.	Hydrocortisone ointment justified and frequently effective. Internal therapy very rarely, only in cases with secondary contact dermatitis.
Lichen planus	Rarely effective.	Not recommended.
Alopecia areata	Quite effective in producing temporary partial regrowth of hair.	Not justified.
Postherpetic neuralgia	Uncertain.	Preliminary trial of other methods preferable.
Lepra reaction	Evidence for some effectiveness accumulating.	Dependent upon judgment of physician experienced in leprosy.
Dermatomyositis	Rarely.	Probably always worthy of trial.
Diffuse scleroderma	Variable.	Not clear-cut. Considerable difference of opinion.
Leukemia with cutaneous manifestations	Rarely effective.	No set opinion possible.
Hodgkin's Disease	Rarely.	No general statement possible.
Dermatitis herpetiformis.	Rarely effective.	Not recommended.
Keloids	Doubtful.	Not recommended.
Chronic urticaria	Most uncertain. Permanent good results uncommon.	Not recommended.

A natural outgrowth of the discovery of the cutaneous effects of systemic steroidal therapy was the study of the action of these hormones when topically applied. Early experience demonstrated that cortisone ointments were

without effect. However, Sulzberger & Witten (29) in 1952 reported some preliminary data which indicated that locally applied hydrocortisone might be active in counteracting certain skin diseases. In addition to three further reports from this group, at least six additional papers have appeared relating clinical experience with hydrocortisone ointments (30 to 38). Certain consistent findings are apparent in these accounts, most of which are in keeping with our personal experience with topical hydrocortisone in the treatment of over 600 patients with various skin diseases (39).

Despite an inability to make more than preliminary generalizations at this time, it seems advisable to list some of the salient features of the experience to date.

(a) Hydrocortisone is best applied topically in an ointment in a concentration of 2.5 per cent. Despite knowledge that effectiveness varies with different bases, the optimal base has not been clearly defined. Furthermore, little investigation has been made of the action of concentrations above 2.5 per cent because of the prohibitive feature of current cost.

(b) Hydrocortone ointment has a definite and striking local anti-inflammatory effect in certain instances. At times this effect may be so immediate and profound as to exceed that observable with any other type of topical medication. The action is however only morbidostatic[2]; discontinuance may result in a prompt recurrence.

(c) Topical hydrocotrisone therapy is without any demonstrable systemic effects. This adds greatly to its value in patients in whom systemic steroids are contraindicated. In contrast to many preparations, hydrocortisone ointment is odorless, colorless and nonirritating.

(d) Topical hydrocortisone would appear to be the initial treatment of choice in the following conditions: (i) perianal or perivulvar pruritus (idiopathic); (ii) localized neurodermatitis; (iii) pyogenic granuloma; (iv) eczematoid reaction of eyelids or ears.

(e) Topical hydrocortisone therapy is of some, though lesser, value in the following dermatologic conditions (in many instances it fails to alter the course of the disease; in others, the cost of medication is prohibitive because of large areas of skin change): (i) atopic dermatitis; (ii) patchy eczematoid contact-type dermatitis; (iii) seborrheic dermatitis (intertriginous); (iv) nummular eczema.

(f) Topical hydrocortisone therapy appears to be valueless in all of the other skin diseases in which it has been used, such as psoriasis, acne, verrucae, and chronic discoid lupus erythematosus.

Further study is needed to delimit the precise role of topical hydrocortisone in dermatologic management. Moreover, there is need for further knowledge regarding the mechanism of action. Are any other adrenal steroids active locally? What physiologic factors favor a therapeutic response? Are other vehicles or higher concentrations likely to enhance their effectiveness? The

---

[2] Term suggested by Sulzberger (29).

vistas of future endeavor are clearly visible, and they promise much of both theoretical and practical account.

Antimalarial compounds in the treatment of chronic discoid lupus erythematosus and polymorphous light eruptions.—The treatment of chronic discoid lupus erthematosus has long been unsatisfactory. A wide variety of treatments have been used, including injections of gold salts, arsenicals and bismuth, local destructive measures, and a variety of local applications. Although these methods of treatment have long been "standard," the reviewers have serious doubts that they are really effective. In 1951, Page (40) reported the results of treatment of eighteen patients with chronic discoid lupus erythematosus with mepacrine hydrochloride in various doses. Some of the patients received 100 mg. daily by mouth, whereas others received as high as 300 mg. daily. In nine of the patients the results were excellent, in five they were good, and in three there was slight improvement. Page reported only mild side effects in his series of patients, including some nausea and vomiting, diarrhea, giddiness, headache, and depression. He theorized that mepacrine might be effective in chronic discoid lupus eryhtematosus by reducing the sensitivity of the skin to light, by a an action similar to that of ACTH or cortisone, or by antagonizing adenyl compounds. This report was original, and not based on any previous work. However, as pointed out in the *1952 Yearbook of Dermatology* (41), the use of quinacrine (Atabrine) for the treatment of chronic discoid lupus erythematosus had been reported in an obscure journal in 1940 by a Russian physician, Prokeptchauk (42). Cure of 35 patients with this disease was reported following the administration of 100 mg. of quinacrine three times daily for ten days, with repeated similar courses. Following Page's original report, a number of reports on this method of treatment have appeared from America and Britain (43 to 46).

The most extensive series of cases, 100, was that reported by Black (47). His results are conservatively expressed. Complete involution occurred in some 17 per cent of his patients, and considerable improvement in 28 per cent There was moderate to slight improvement in 25 per cent and the eruption was unchanged or worse in 30 per cent. Lichenoid atabrine dermatitis occurred in two patients, once after 100 mg. twice daily for 15 weeks, and in the other after 100 mg. three times daily for 16 weeks.

The results of quinacrine therapy, though by no means completely satisfactory, represented a considerable improvement over anything previously available. The pigmentation is a highly objectionable feature to many patients. Of more importance are the possible side reactions, which were seen in large numbers of patients during World War II, and which include lichenoid dermatitis, aplastic anemia, and hepatitis. Custer has reported a total of 57 fatal cases of aplastic anemia attributable to quinacrine occurring in U. S. Armed Forces in the Southwest Pacific (48). This fatal reaction to therapy occurred among troops who were receiving 100 mg. of quinacrine daily for long periods of time.

Parimer & Sawitsky (49) have reported a patient who died of aplastic

anemia four months after institution of quinacrine therapy in a dose of 1 gm. (sic) twice daily. (In all probability this is a misprint, and the dose received was 0.1 gm. twice daily.) Treatment was apparently continued for approximately three months. The evidence that quinacrine was responsible for the development of aplastic anemia in this patient is quite convincing.

Because of the known capacity of quinacrine to produce serious reaction when administered over a prolonged period of time, the reviewers have employed such therapy in very few patients. Chloroquin is an antimalarial without the objectionable feature of producing pigmentation of the skin and with, to date, a good record in respect to serious reactions to treatment. During the past year we have employed such therapy in 16 patients with chronic discoid lupus erthematosus with excellent results in ten (50). Goldman et al. (51) reported their short-term results in 18 patients with discoid lupus erythematosus, 11 of them showing great improvement. One patient was unable to continue therapy because of repeated nausea and emesis, and abdominal cramps and diarrhea were also noted. The dose employed was ordinarily 0.25 gm. twice daily for one or two weeks, followed by 0.25 gm. daily for four to six weeks. We have ordinarily given a dose of 0.25 gm. daily initially, with reduction of the dose to every other day, or even less frequently, as soon as marked improvement has been obtained.

It may be concluded that antimalarial compounds have a definite beneficial effect on most patients with chronic discoid lupus erythematosus. The reviewers doubt that the use of quinacrine is justifiable for this disease which, though extremely chronic and productive of marked scarring, is essentially benign. Whether or not chloroquin will prove to be the drug of choice, or whether more extensive experience with it will uncover serious reaction-producing capacity, is yet to be determined.

A study was made by Cahn et al. (52) on 16 patients to determine the effectiveness of chloroquine diphosphate (aralen) and quinacrine (atabrine) hydrochloride in preventing the development of the prurigo aestivalis type of polymorphous light eruptions. These patients gave a history of recurrent eruptions of this type in the spring and summer on the sun-exposed regions of the body, for from 2 to 19 years. Despite unrestricted sun exposure, 14 of these 16 patients had no recurrences for the remainder of the summer months while taking chloroquine or quinacrine.

TREATMENT OF FUNGOUS INFECTIONS[3]

Superficial fungous infections.—Although hundreds of antifungal agents are known, for the most part their value has not been shown by critical clinical investigations. The perfect agent for the treatment of the superficial fungous infections is not yet at hand and the search must go on. Fatty acids remain the treatment of choice, though they are far from effective, and their chief virtue lies in their low irritant and sensitizing powers.

[3] We are indebted to Dr. Albert M. Kligman for the material on which this section is based.

The systemic mycoses and their treatment.—Drug therapy of this hetero-
geneous group of diseases is unsatisfactory. Evaluation of recently developed
chemotherapeutic agents is incomplete, though it seems certain that at least
a few of these mycoses are now amenable to treatment. Therapeutic experi-
ence is necessarily limited by the rarity of those progressive conditions for
which treatment is required. Thus, the remarks which are to follow have a
provisional character and may require revision when our knowledge of this
subject is more complete.

The principal systemic mycoses are histoplasmosis, coccidioidomycosis,
blastomycosis, South American blastomycosis, sporotrichosis, moniliasis,
torulosis, actinomycosis, and nocardiosis. Although moniliasis may be a fatal
disseminated disease, it usually presents only muco-cutaneous signs. Thrush
of the oral mucous membranes is its commonest expression. As a superficial
disease, it is managed chemotherapeutically in the same manner as the super-
ficial fungous infections. A moderately effective remedy is 1 to 2 per cent
aqueous gentian violet.

Chemotherapeutic agents.—(a) Potassium iodide. Folkore attributes to this
drug greater therapeutic attributes against fungous infections than it actually
deserves. Indeed, sporotrichosis is the only mycosis which regularly responds
to iodide therapy. Whether or not certain forms of cutaneous blastomycosis
are beneficially influenced is moot. Iodides are ineffective in coccidioido-
mycosis, histoplasmosis, actinomycosis, moniliasis, and torulosis. Strictly
speaking, potassium iodide is not a chemotherapeutic agent. It has no anti-
fungal properties whatever. Its mode of action is unknown. Evidently there
is an interference with the host reaction to the parasite. Enormous quantities
of iodide may be given before signs of iodism develop. The dosage schedule is
not fixed, and large quantities are required for a relatively long period of
time. It is a good idea gradually to increase the dose till the point of tolerance
is reached. The initial dose may be 10 drops of saturated potassium iodide
three times daily; thereafter, each of the three daily doses is increased by
one drop per day; that is, 11 drops three times a day would be given on the
second day, etc. There is no point in increasing the dose beyond 100 drops
three times daily if the level of tolerance has not been reached with that dos-
age. Iodide administraion should be continued for a period of at least a few
weeks even after all clinical signs of active infection have resolved; that is,
even after "complete" healing has taken place.

(b) Ethyl vanillate. This is a colorless crystalline solid which is insoluble
in water and has a cinnamon-like taste. Chemically, it is 4-hydroxy-3-
methoxy-benzoate. *In vitro* tests show it to be inhibitory for most of the path-
ogenic fungi, including the superficial ones, in concentrations ranging from
100 to 500 μg. per ml. (53). It is thus a relatively potent antifungal agent.
The therapeutic blood level probably is of the order of 20 to 30 mg. per 100
ml. A chemical method of blood assay is available. The drug is readily ab-
sorbed after ingestion. In man peak levels are reached three to four hours
after oral administration and are maintained for five to six hours. Blood

levels in excess of 50 mg. per ml. may cause toxic reactions such as nausea and vomiting, drowsiness, apathy, hyperpnea, and acidosis. Most of the drug is excreted rapidly via the kidney, either as ethyl vanillate or a conjugate. Appreciable amounts pass the meningeal barrier and accumulate in the spinal fluid.

The toxicity of this agent is quite low. Guinea pigs will tolerate as much as a 1000 mg./kilo daily by oral administration, whereas rabbits can take three times as much for a period of several weeks. Oral doses of 30 to 45 gm. per day in humans for periods of 3 to 18 months produce occasional mild nausea, acidosis, hyperpnea, or episodes of shock. The incidence and severity of toxic reactions increase when 100 gm. is given daily for several months. Such doses are, however, entirely feasible with carefully managed patients. Hepato-renal damage may result when large amounts are given for periods of a month or more. Forty-five gm. daily have been given to some patients for as much as a year without serious consequence.

Preliminary studies indicate that ethyl vanillate may be therapeutically useful in the disseminated forms of histoplasmosis and coccidioidomycosis. The data supporting this view are, however, far from complete (54). Other deep fungi are sensitive to ethyl vanillate *in vitro*. Perhaps the drug will be found useful in treating other mycoses. The recommended dosage approaches the limit of tolerance. In adults, 45 gm. per day orally in four to six divided doses is approximately the desired amount. It is well to begin with 15 gm. per day and gradually increase the dosage according to the tolerance of the patient. Ideally, the blood levels should be followed. Since this is impractical, the clinical and biochemical responses of the patient must be watched closely. A course of treatment generally requires six weeks or longer, depending on the clinical effects which are achieved. Rapid improvement is not to be anticipated. Months of daily treatment may be required. The drug should be given after meals to reduce gastric irritation.

(c) The aromatic diamidines. The trypanocidal activity of these compounds has been appreciated for a long time. Recently, propamidine, stilbamidine, and pentamidine have been shown to have antifungal properties. Stilbamidine has proved decidedly encouraging in the treatment of blastomycosis (55). Intensive study of this and related compounds gives promise of developing potent therapeutic agents against blastomycosis and perhaps other systemic mycoses. Experience with these agents has not yet been extensive enough to present more than a provisional account. The superficial and deep fungi as a group are inhibited by propamidine, stilbamidine and pentamidine. These compounds have approximately similar potency in laboratory tests, although propamidine is slightly more potent. Whereas some investigators report inhibition of some fungi with a few μg. per ml. of medium, others indicate the minimal inhibiting concentration to be as high as 1000 μg. per ml. (56). Strain variability and differences in testing techniques may account for these differences. Early (and inadequate) therapeutic experience with stilbamidine in histoplasmosis and cryptococcosis has not been encour-

aging, even though the causative organisms are quite sensitive *in vitro*. The mycoses other than blastomycosis, which will be benefited by these agents, still remain to be determined. Stilbamidine to date has seemed preferable to propamidine and pentamidine.

Stilbamidine is a white crystalline powder which is quite soluble in water. Unless kept in the dark the solution is unstable; the degradation products which accumulate in solutions on standing are quite toxic. Hence, fresh solutions must be used.

The dosage schedule has not been precisely fixed. A total amount of 4.5 to 6.0 gm. is probably adequate for most cases. Preferably, a 10 to 14 daily course of treatment is given with a free period of two to four weeks before the next course is started. Usually two to three such courses suffice. The clinical response as well as the drug tolerance of the patient will control the actual routine of drug administration and the degree to which the arbitrary schedule given above can be modified. An acceptable program is as follows:

1st day	0.05 gm. I.V. in 100 cc. of 5 per cent glucose solution
2nd day	0.10 gm. I.V. in 100 cc. of 5 per cent glucose solution
3rd day to 14th day	0.150 gm. I.V. in 500 cc. of 5 per cent glucose solution

The patient is allowed to rest two to four weeks and a similar course is again given. If there has been insufficient response or relapse, further courses can be given after rest periods of a month or more. On the other hand, others have given a total dose of 4.0 gm. in a single course of daily intravenous injections for a month.

Signs of hepatic and renal damage should be watched for. A delayed trigeminal neuralgia is a peculiar and sometimes quite distressing complication in a good percentage of cases. This has not been disabling and is not an absolute contraindication to treatment.

There is a striking structural similarity between stilbamidine and diethylstilbestrol. This latter agent has been found to be even more fungistatic *in vitro* than stilbamidine. Several patients with cutaneous blastomycosis were greatly benefited by small daily doses of stilbestrol (1 mg. three times daily). This finding may open up new paths of investigation with the steroid hormones. The therapeutic effectiveness of stilbestrol may not reside entirely in its antifungal properties.

Antifungal antibiotics.—Of the many antifungal antibiotics which are known, only two seem worthy of mention. The others are either too toxic or have failed to exhibit any protective effect in experimentally infected animals. The following information is subject to considerable qualification because of a very limited experience in humans. These agents are purely in the experimental stage. A great deal remains to be learned about their pharmacology, toxicity, clinical effectiveness, and chemical purification.

Fungicidin (*Nystatin, Squibb*).—This antibiotic is produced by Streptomyces noursei (57). It occurs as a fine yellow powder sparingly soluble in water. The dry powder is reasonably stable in the cold as are aqueous solu-

tions of pH 7.0. Gastric juice inactivates fungicidin. Correlatively, the aqueous solution at pH 2 is known to be unstable. Simultaneous administration of a buffer is indicated for oral use. Fungicidin is fungistatic and fungicidal. Its activity is completely reversed by cysteine, although serum has no appreciable effect. Most of the pathogenic fungi are inhibited by amounts of less than 10 μg. per ml. of medium. Fungicidin has no bacteriostatic effects. Fungistatic blood levels may be obtained following oral administration. Little is known about absorption and excretion although there is evidence that the agent persists in good concentration in the blood for as much as 24 hr. after a single dose.

The acute L.D. 50 for intraperitoneally injected mice is only about 25 mg./kilo. Much larger quantities are tolerated subcutaneously and orally. Fungicidin is not yet available in a highly purified form. Figures on toxicity are accordingly unreliable. The intramuscular injection into rabbits of 0.5 per cent solutions causes degenerative changes.

Preliminary studies indicate that fungicidin exerts a protective effect in experimental cryptococcosis, histoplasmosis, moniliasis, and particularly coccidioidomycosis. Experimental studies in humans have not yet accumulated. Dosage will have to be worked out empirically. Oral administration along with suitable buffers against gastric acids is evidently feasible. The drug is too irritating for subcutaneous or intramuscular injection. Intravenous infusion by slow drip is a possible route of administration.

Candicidin.—This antibiotic is elaborated by a member of the Streptomyces griseus group. Candicidin A and B are the water soluble or water dispersible fractions which are of therapeutic interest (58). Candicidin is relatively unstable in aqueous solutions and is largely inactivated at acid pH's. This antibiotic is appropriately named in recognition of its great inhibitory potency against Candida species. Concentrations of 0.5 to 10 μg. per ml. are inhibitory for Candida species, Blastomycoses, Histoplasma, and Cryptococcus. Curiously, filamentous molds such as Coccidioides and all of the ringworm species are resistant to its action. Candicidin is fungicidal as well as fungistatic. Bacteria are insensitive. Presently available samples are impure. The acute L.D. 50 for intraperitoneally injected mice is about 65 mg./kilo. The 1 per cent solution causes necrosis when injected subcutaneously. The drug is not absorbed after oral administration. Protective effects in experimental moniliasis, blastomycosis and sporotrichosis in mice have been demonstrated. Presumably, intravenous infusion would be the only means of administering this antibiotic to humans. Nothing is known about dosage or toxicity for humans.

DISEASES OF THE ECCRINE SWEAT GLAND

In clinical dermatology, simple inspection will often enable one to characterize an eruption as arising primarily from the dermis (connective tissue), or the epidermis (epithelial cells), or from the hair follicle and sebaceous gland unit. This can be done because of gross anatomic reference points. In

contrast, the eccrine sweat gland unit is not clinically identifiable and, accordingly, many disorders of this gland have been unknowingly lumped in with those of the general epidermis. It is only recently that histologic and physiologic studies have clearly indicated that the sweat gland plays an important role in (a) the initiation of skin disease; (b) the secondary aggravation of the severity of pre-existing dermatoses; and (c) the medical economy of patients with widespread skin lesions.

Despite a wide range of clinical signs, symptoms, and effects, all of the findings in clinical disorders of sweating may have a single common denominator: the secretion of sweat in the presence of occlusion of the sweat pore.

As early as 1800 the problem of retention of sweat attributable to plugging of the gland openings was critically discussed. Actually, many disease processes were specifically noted as showing local or general anhidrosis presumably on this basis. However, the only skin lesion directly attributable to sweat retention was sudamina or miliaria crystallina. This was seen in numerous febrile patients and, in 1884, Robinson stressed the fact that the sudaminal vesicle resulted from trapped sweat (59). Later, in 1893, Pollitzer claimed that miliaria rubra or prickly heat was also attributable to sweat retention (60). Despite the excellence of his studies and histologic findings, his view was never widely accepted, since clinicians found it difficult to conceive of unit anhidrosis in the presence of diffuse hyperidrosis. Actually, Pollitzer's views on the miliarial group of diseases were over a half century before their time. He clearly described miliaria as appearing in three distinct clinical forms, resulting from loci of sweat retention at three different levels in the skin (61).

Pollitzer's work was disregarded, and studies on miliaria for the next 50 years largely centered about sporadic therapeutic trials. It was not until World War II that interest and clinical experience ran high in skin disorders of the hot climates. With amazing rapidity the concept of sweat retention as the mechanism of miliaria received experimental support and clinical confirmation from world-wide sources.

Clinically, it was discovered that there was a new type of heat exhaustion or asthenia occurring in troops exposed to high temperatures, either in the desert or in the tropics (62, 63, 64). This manifested itself by lassitude, weakness, elevation of temperature, and signs of heat intolerance. From the skin standpoint, it was found that, although such individuals showed normal or excessive sweating of the face, the skin elsewhere was absolutely dry and anhidrotic. Moreover, this anhidrotic skin developed peculiar small papules whenever the subject engaged in severe physical effort. Allen & O'Brien were the first to delineate both the clinical picture and the etiology of this new entity (65). By careful study they could demonstrate that sweat gland occlusion was responsible for the anhidrosis and for the appearance of the skin lesions. O'Brien was able to show conclusively that the papules each represented collections of trapped sweat.

Sulzberger and his colleagues in a series of papers also confirmed this and

proved that sweat retention was responsible for the lesions of miliaria rubra (prickly heat) (66, 67). On the basis of this work by O'Brien and by Sulzberger's group, it could be demonstrated that the lesions of tropical anhidrotic asthenia actually were a late stage of miliaria. It was found that the "level of sweat escape into the skin" determined the clinical pattern. Thus, in miliaria crystallina (or sudamina) the sweat is retained in the superficial stratum corneum, in miliaria rubra it collects in the deeper epidermis after rupture of the intraepidermal sweat duct and, finally, in the lesion of tropical asthenia it occurs just below the epidermis. Because of this deeper level of escape, we have elected to name the skin changes miliaria profunda (68). Other observers have called them mammilaria (because of the mammilated appearance of the skin), or miliaria alba (alluding to the light color) (69, 70). In view of the common etiologic story, we stress the value of the generic term miliaria.

In 1952, Lobitz added an important member to the clinical family of miliaria (71). He described a special type of miliaria seen as a complication of numerous skin diseases. Clinically it manifests itself as pruritic pustules. Each pustule is the seat of sweat retention with secondary leucocytic infiltration.

Sulzberger's group has been active in showing that sweat retention is responsible for many of the flares and exacerbations of a wide variety of dermatidides seen in hot weather (72). Here, secondary miliaria may or may not be clearly evident. Moreover, they have stressed the medical significance of a general failure to deliver sweat to the skin surface. Heat intolerance, with all its manifold signs, can result just as surely from occluded sweat glands as from a primary failure of the gland to secrete.

Experimental production of miliaria has been studied by Shelley and his colleagues (73 to 77), O'Brien (78), Thomson (79), and Sulzberger et al. (80). In a series of papers, Shelley et al., demonstrated that a wide variety of minor epidermal injuries would induce a hyperkeratotic occlusion of the sweat pore. In each instance, local anhidrosis attributable to sweat retention was present. Intensive stimulation of sweating led to the appearance of all types of miliaria, the type dependent upon the depth of injury. Aside from superficial miliaria crystallina, the miliarias or clinical signs appeared only in susceptible subjects.

The wide range of injurious agents is of significance:

electrodesiccation	x-ray
iontophoresis	abrasion
heat	adhesive tape
cold	wet dressing (water)
ultraviolet light	
chemical	
aluminum chloride	
soap	
surface active agents (80)	

turpentine
phenol
nitric acid
chloroform
kerosene (78)
mustard plaster (79)

None of these agents, in the manner used, affect the secretory acini of the sweat gland. All of the changes were produced in the epidermis.

As a result of these recent studies, it is now possible to unify all miliarias on the basis of a common pathogenesis (81). In the "primary" types of miliaria, prolonged maceration of the skin surface by sweat serves to produce a minor nonspecific epidermal injury. Subsequent abnormal keratinization occludes the sweat pore with resultant sweat retention. In susceptible individuals, rupture of the duct then occurs at various points, permitting seepage of sweat into the skin and the development of attending signs. Secondary miliaria may be viewed as the same process occurring in areas of skin in which occlusion of the pore has occurred as a result of a preceding dermatitis.

URTICARIA PIGMENTOSA

In 1869, Nettleship described a unique urticarial eruption in a two-year-old girl. "The eruption was peculiar in leaving stains of a light brown colour" (82). During the following 85 years a rather complete clinical entity came to be recognized, but only in the last year has the physiology of this disease been clarified. This physiologic insight has resulted from the efforts of a wide group of investigtors who have centered their study on the mast cell.

Urticaria pigmentosa must tell the story of the mast cell, since each lesion is actually a tumor or overabundance of mast cells. Clinically, the urticaria pigmentosa lesions show selective urticaria or swelling as the result of any mechanical irritation. Coincidentally, the mast cells discharge their granules (83). The time relations have suggested that the granules are composed of a substance responsible for the urticaria. To review our knowledge of the mast cell, in 1937 Jorpes (84) showed conclusively that the mast cells of the liver contained large amounts of heparin. Recently, Urbach and his colleagues (85) have shown that the blood level of circulating heparin increases greatly in patients with urticaria pigmentosa whenever the lesions are mechanically stimulated. This temporary rise corresponds in magnitude to that seen following the injection of 50 mg. of heparin intramuscularly. The clotting and bleeding time remain normal. Yet, this heparinemia suggests strongly that heparin may play a role in the urticaria pigmentosa patients with local purpura.

Heparin itself is not urticariogenic (86), and attention must be directed elsewhere for the explanation of the chief sign of urticaria pigmentosa. By means of ultra-centrifugation studies, Sylven found that the mast cell granule actually has a surface film of unknown composition over its core of heparin (87).

Riley & West (88) and Graham *et al.* (89) have gathered data showing that the mast cell contains about 1 per cent histamine. The granules thus appear to be a histamine-heparin complex. This finding has revealed the cause of the urticaria since histamine is a most powerful urticariogenic agent. Tremendous amounts of histamine are released at the time of mast cell stimulation, since complete dissolution of the granules may occur. Significantly, oral antihistaminics are of no avail therapeutically, since these high tissue histamine levels are not matched by similar tissue antihistamine levels after oral dosage. On occasion, intravenous antihistamines might be expected to have some neutralizing effect, as apparently was seen by Saunders (90). Local injection of antihistaminics is also of no value since the trauma of injection discharges all of the mast cell "secretion."

As a result of these recent studies, it is possible to explan the urticaria of this unusual disease on the basis of histamine liberation, the occasional purpura on the basis of heparin, and the pigmentation possibly as the result of stimulation of the overlying epidermal melanocytes by repeated exposure to histamine and/or heparin.

From the therapeutic standpoint, "DOCA" (desoxycorticosterone acetate) is now being tried experimentally in man (85), since in rats continued administration of this hormone leads to the complete disappearance of the tissue mast cells (91). Certainly, cortisone and ACTH also hold promise for the therapy of severe urticaria pigmentosa, since these agents also have a lytic effect on the mast cell (92). Recently, Bloom (93) has induced complete involution of mast cell tumors in dogs by cortisone therapy.

LITERATURE CITED

1. Pillsbury, D. M., and Urbach, F., In *Medical Uses of Cortisone* (Lukens, F. D. W., Ed., The Blakiston Co., Philadelphia, Pa., in press)
2. Brown, E. A., *Ann. Allergy*, **10**, 508 (1952)
3. Leith, W., Graham, M. J., and Burrage, W. S., *J. Allergy*, **22**, 99 (1951)
4. Long, J. B., and Favour, C. P., *Bull. Johns Hopkins Hosp.*, **87**, 186 (1950)
5. Sulzberger, M. B., Sauer, G. C., Herrmann, F., Baer, R. L., and Milberg, I. L., *J. Invest. Dermatol.*, **16**, 323 (1951)
6. Shwartzman, G., Schneierson, S. S., and Soffer, L. J., *Proc. Soc. Exptl. Biol. Med.*, **75**, 175 (1950)
7. Harris, S., and Harris, T. N., *Proc. Soc. Exptl. Biol. Med.*, **74**, 186 (1950)
8. Castor, C. W., and Baker, B. L., *Endocrinology*, **47**, 234 (1950)
9. Goldman, L., Preston, R., and Rockwell, E., *J. Invest. Dermatol,.* **18**, 89 (1952)
10. Ehrich, W. E., *Am. Heart J.*, **43**, 121 (1952)
11. Hopkins, J. G., Kesten, B. M., Nelson, C. T., Hambrick, G. W., Jr., Jennings, R. G., Jr., and Machacek, G. F., *Arch. Dermatol. Syphilol.*, **65**, 401 (1952)
12. Kierland, R. R., O'Leary, P. A., Brunsting, L. A., and Didcoct, J. W., *J. Am.Med. Assoc.*, **148**, 23–26 (9152)
13. Soffer, L. J., and Bader, R., *J. Am. Med. Assoc.*, **149**, 1002–8 (1952)
14. Brunsting, L. A., Slocumb, C. H., and Didcoct, J. W., *Arch. Dermatol. Syphilol.*, **63**, 29–48 (1951)

15. Haserick, J. R., Corcoran, A. C., and Dunstan, H. P., *J. Am. Med. Assoc.*, **146**, 643–45 (1951)
16. Irons, E. N., Ayers, J. P., Brown, R. G., and Armstrong, S. H., Jr., *J. Am. Med. Assoc.*, **145**, 861–69 (1951)
17. Lever, W. F., *New Engl. J. Med.*, **245**, 359–63 (1951)
18. Blank, H., *Penn. Med. J.*, **54**, 1062–65 (1951)
19. Moore, J. E., and Mohr, C. F., *J. Am. Med. Assoc.*, **150**, 467–73 (1952)
20. Haserick, J. R., and Long, R., *Ann. Internal Med.*, **37**, 559–65 (1952)
21. Lever, W. F., *Medicine*, **32**, 1 (1953)
22. Blank, H., and Burgoon, C. F., *J. Invest. Dermatol.*, **18**, 213 (1952)
23. Wammock, V. S., Biederman, A. A., and Jardon, R. S., *J. Am. Med. Assoc.*, **147**, 637–39 (1951)
24. Pillsbury, D. M., *Proc. Intern. Congr. Dermatol.*, 10th Congr. (Brit. Med. Assoc., London, England, 556 pp., 1953)
25. Sternberg, T. H., Newcomer, V. D., and Linden, J. H., *J. Am. Med. Assoc.*, **148**, 904–5 (1952)
26. Folk, M. S., Allende, M. F., and Bennett, J. H., *J. Invest. Dermatol.*, **18**, 307–10 (1952)
27. Way, L. N., and Murgatroyd, G. W., *J. Allergy*, **23**, 215 (1952)
28. Sulzberger, M. B., Sauer, G. C., Herrmann, F., Baer, R. L., and Milberg, I. L., *J. Invest. Dermatol.*, **16**, 323 (1951)
29. Sulzberger, M. B., and Witten, V. H., *J. Invest. Dermatol.*, **19**, 101 (1952)
30. Sulzberger, M. B., *The Yearbook of Dermatology* (Year Book Publishers, Chicago, Ill., 444 pp. 1953)
31. Sulzberger, M. B., *Arch. Dermatol. Syphilol.*, **58**, 451 (1953)
32. Sulzberger, M. B., Witten, V. H., and Smith, C. C., *J. Am. Med. Assoc.*, **151**, 468 (1953)
33. Rein, C. R., *Arch. Dermatol. Syphilol.*, **58**, 452 (1953)
34. Alexander, R. M., and Manheim, S. D., *J. Invest. Dermatol.*, **21**, 223 (1953)
35. Goldman, L., and Preston, R. H., *Arch. Dermatol. Syphilol.*, **67**, 163 (1953)
36. Goldman, L., Preston, R., and Rockwell, E., *J. Invest. Dermatol.* **18**, 89 (1952)
37. Robinson, R. C. V., *Bull. Johns Hopkins Hosp.*, **93**, 147 (1953)
38. Heilesen, B., Kristjansen, A., and Reymann, F., *Arch. Dermatol. Syphilol.* (In press)
39. Pillsbury, D. M., Bikle, C. A., and Shelley, W. B., *Arch. Dermatol. Syphilol.* (In press)
40. Page, F., *Lancet*, **II**, 755–58 (1951)
41. Sulzberger, M. B., and Baer, R. L., *The Yearbook of Dermatology* (Yearbook Publishers, Chicago, Ill., 444 pp., 1952)
42. Prokeptchauk, A. J., *Vestnik. Venerol. i Dermatol.*, **213**, 23–26 (1940)
43. Sommerville, J., Devine, B. C., and Lagan, J. C., *Brit. J. Dermatol.*, **64**, 417–19 (1952)
44. Sawicky, H. H., Kanof, N. B., Silverberg, M. G., Braitman, M., and Kalish, B., *J. Invest. Dermatol.*, **19**, 397–404 (1952)
45. Wells, G. C., *J. Invest. Dermatol.*, **19**, 405–7 (1952)
46. Cramer, J. C., and Lewis, G. M., *J. Invest. Dermatol.*, **19**, 393–95 (1952)
47. Black, H., *Brit. J. Dermatol.*, **65**, 195–203 (1953)
48. Custer, R. P., *Am. J. Med., Sci.*, **212**, 211–24 (1946)

49. Parimer, L. G., and Sawitsky, A., *J. Am. Med. Assoc.*, **153**, 1172–74 (1953)
50. Pillsbury, D. M., and Jacobson, C., *J. Am. Med. Assoc.* (In press)
51. Goldman, L., Cole, B. P., and Peeston, R. H., *J. Am. Med. Assoc.*, **152**, 1428 (1953)
52. Cahn, M. M., Levy, E. G., and Shaffer, B., *J. Invest. Dermatol.* (In press)
53. Cohen, R., *Arch. Pediat.*, **68**, 259–64 (1951)
54. Christie, A., Middleton, J. G., Peterson, J. C., and McVickar, D. L., *Pediatrics*, **7**, 7–15 (1951)
55. Schoenbach, E. B., Miller, J. M., and Long, P. H., *Ann. Internal Med.*, **37**, 31–47 (1952)
56. Bocobo, F. C., Curtis, A. C., and Harrell, E. R. (In press)
57. Hazen, E. L. and Brown, R., *Proc. Soc. Exptl. Biol. Med.*, **76**, 93–96 (1951)
58. Kligman, A. M., and Lewis, F. S., *Proc. Soc. Exptl. Biol. Med.*, **82**, 399–404 (1953)
59. Robinson, A. R., *J. Cutaneous and Venereal Diseases*, **2**, 362 (1884)
60. Pollitzer, S., *J. Cutaneous Genito-Urinary Diseases*, **11**, 50 (1893)
61. Pollitzer, S., *N. Y. Med. J.*, 59, 12 (1894)
62. Ladell, W. S. S., *Brit. Med. Bull.*, **3**, 735 (1945)
63. Allen, S. D., and O'Brien, J. O., *Med. J. Australia*, **2**, 335 (1944)
64. Walkin, J., Goodman, J. I., and Kelley, W. E., *J. Am. Med. Assoc.*, **124**, 478 (1944)
65. O'Brien, J. P., *Brit. J. Dermatol. and Syphilol.*, **59**, 125 (1947)
66. Sulzberger, M. B., Zimmerman, H. M., and Emerson, K., Jr., *J. Invest. Dermatol.*, **7**, 153 (1946)
67. Sulzberger, M. B., and Zimmerman, H. M., *J. Invest. Dermatol.*, **7**, 61 (1946)
68. Shelley, W. B., Horvath, P. N., and Pillsbury, D. M., *Medicine*, **29**, 195 (1950)
69. Horne, G. O., and Mole, R. H., *Trans. Roy. Soc., Trop. Med. Hyg.*, **44**, 465 (1951)
70. Horne, G. O., and Mole, R. H., *Trans. Roy. Soc. Trop. Med. Hyg.*, **45**, 399 (1951)
71. Lobitz, W. C., *J. Am. Med. Assoc.*, **148**, 1097 (1952)
72. Sulzberger, M. B., and Herrmann, F., *The Clinical Significance of Disturbances in the Delivery of Sweat* (Charles C Thomas, Publisher, Springfield, Ill., 1953)
73. Shelley, W. B., Horvath, P. N., Weidman, F. D., and Pillsbury, D. M., *J. Invest. Dermatol.*, **11**, 275 (1948)
74. Shelley, W. B., and Horvath, P. N., *J. Invest. Dermatol.*, **14**, 9 (1950)
75. Shelley, W. B., and Horvath, P. N., *J. Invest. Dermatol.*, **14**, 193 (1950)
76. Shelley, W. B., *J. Invest. Dermatol.*, **16**, 53 (1951)
77. Shelley, W. B., *J. Invest. Dermatol.* (In press, 1953)
78. O'Brien, J. P., *J. Invest. Dermatol.*, **15**, 95 (1950)
79. Thomson, M. L., *J. Physiol. (London)*, **112**, 31 (1951)
80. Sulzberger, M. B., Herrmann, F., Keller, R., and Pisha, B. V., *J. Invest. Dermatol.*, **14**, 91 (1950)
81. Shelley, W. B., *J. Am. Med. Assoc.*, **152**, 670 (1953)
82. Nettleship, E., *Brit. Med. J.*, **II**, 323 (1869)
83. Wilander, O., *Arch. Physiol.*, **81**, Suppl. 15 (1938)
84. Jorpes, J. E., *Heparin in the Treatment of Thrombosis*, 2nd. ed. (Oxford University Press, London, England, 260 pp., 1946)
85. Urbach, F., Jacobson, C., and Bell, W. G. (In press)
86. Shelley, W. B., and Blank, H. (Unpublished data)
87. Sylven, B., *Acta Physiol. Scand.*, **19**, 289 (1950)

88. Riley, J. F., and West, G. B., *J. Physiol. (London)*, **120**, 528 (1953)
89. Graham, H. T., Lowry, O. H., Wahl, N., and Pricbat, M. K., *Proc. Intern. Physiol Congr.*, 19th Congr., Montreal, Canada, 1953
90. Saunders, T. S., and Miller, O. G., *J. Invest. Dermatol.*, 11, 309 (1948)
91. Stuart, E. G., *Studies of the Mast Cell* (Doctoral thesis, University of Pennsylvania, Philadelphia, Pa., 1952)
92. Smith, D. E., and Lewis, Y. S., *Proc. Intern. Physiol., Congr.*, 19th Congr., Montreal, Canada, 1953
93. Bloom, F., *Proc. Soc. Exptl. Biol. Med.*, **79**, 651 (1952)

PEDIATRICS[1]

By James L. Wilson[2]

Department of Pediatrics and Communicable Diseases, University Hospital,
University of Michigan, Ann Arbor, Michigan

Introduction

The subject of pediatrics is as broad as that of all medicine. It is, of course, all medicine restricted only by a limited age. This short review of pediatric progress is written with no attempt at completeness in respect to the number of subjects covered or in any subject. Matters for discussion are chosen according to the interests of the author and his associates, and personal opinions are sometimes freely expressed.

Such an enormous reduction has been made in infant and child mortality in recent decades that pediatricians now spend a great deal of their time in preventive medicine, more than any other group of physicians who actually care for patients. This has been so true that at times we hear the argument that much less attention in research and education should be directed towards diseases of children and more towards understanding of functional disturbances. However, one needs only to move around the wards of our best hospitals to be impressed by the tragic evidences of medical ignorance and helplessness in the face of disastrous disease. There is, nevertheless, a great change in the incidence of disease with tremendous reduction of bacterial infections. There has been a great reduction in the diarrheal diseases of infancy, and yet epidemic diarrhea of new-born in hospitals and of older infants, too, has seemed to increase in frequency. Since these diseases are a product of medical attention which has increased the incidence of hospitalization of infants, perhaps it is the most important problem that has to be faced by the medical profession.

In the case of virus diseases great increase in knowledge has occurred, but again without such advances that we have effective preventive or therapeutic programs. Poliomyelitis, being the virus disease for which most money is available for study, is the best illustration of what progress has been made and further mention will be made of it.

There has been a great change in the incidence of the causes of death in children. Accidents have become the major cause of death in children of all age groups past one year of age (1, 2, 3). The Bureau of Census for 1945 (4) lists the following distribution of causes of death at three years of age: acci-

dents, 28 per cent; respiratory diseases, including diphtheria, 21 per cent; tumors, 5.3 per cent; and blood dyscrasias, 4.5 per cent.

The growing importance of neoplasms as a cause of childhood mortality should be stressed (1). In all age groups from three to ten years, tumors (including leukemia) occupy one of the first four principal causes of death. The types of neoplasia found differ from those commonly observed in the adult. Tumors of the central nervous system are the most common, followed in order by those of the hematopoietic system (leukemia, lymphoma, Hodgkin's disease), kidney and adrenal areas (Wilm's tumor and neuroblastoma), and bone.

CAUSES OF CONGENITAL ANOMALIES

With decreasing mortality from malnutrition and infection more attention has been directed toward understanding of congenital anomalies (5). It seems that certain maternal infections and exposure to relatively heavy doses of roentgen rays or similar forms of radiation during the first trimester of pregnancy will fairly regularly result in anomalies. The reports of Gregg (6) from Australia in 1942 concerning the high incidence of congenital malformations in children born to mothers who had rubella during early pregnancy stimulated a renewed interest in the problem. The Committee on Congenital Malformations of the American Academy of Pediatrics reported that there were, by 1950, approximately 1000 authentic cases of serious congenital malformation following rubella and 16 cases of defective children out of a total of 86 exposed to various specific infections other than rubella. Important and as yet unanswered questions still remain, such as: how often the fetus may be expected to escape injury and when therapeutic abortion is indicated.

Of the 205 pregnant women studied who were exposed to the irradiation of the atomic bomb at Hiroshima, a total of 28 abnormal infants resulted (7). Those mothers who were closest to the hypocenter produced the largest number of malformed offspring. In this group there were six children with microcephaly and mental retardation and two with mongolism.

Warkany's work with vitamin deficiencies of a severe degree in animals has pointed out that the time at which deficiency occurs, its degree and duration, all play a part in the type of resulting deformity and that under specific conditions the same deformities occur with precise regularity (8). Nearly all tissues have been affected including brain, skull, tongue, limb buds, etc.

The genetic basis of congenital anomalies has long been recognized. A few well established inherited anomalies are brachydactyly, polydactyly, albinism, achondroplasia, and lethal multiple telangiectasia. These anomalies are influenced by all the rules of heredity and occurrence depends upon dominance, penetrance, mutations, etc. Their importance relative to future children by the same parents cannot be overemphasized unless complete genetic studies are indicated.

In addition to those causes already mentioned one might briefly add the following to the list: (*a*) Mechanical factors such as fetal position, causing micrognathia, club foot, etc. and also amniotic bands, ectopia, and oligohydramnios. These factors, because they are more important late in intrauterine life, cause malformations usually of a lesser degree than those previously discussed. (*b*) Endocrine factors are not often implicated. It is known, however, that the incidence of congenital anomalies is six times greater in the diabetic mother than in the normal. The pseudohermaphrodite with associated urogenital anomalies is almost certainly the result of excessive androgenic hormone produced by the fetal adrenal cortex. (*c*) Isoimmunity attributable to Rh incompatibility and the resulting kernicterus is probably a late intrauterine occurrence.

Both in animals and in man similar congenital malformations such as microcephaly result from (*a*) genetic causes, (*b*) irradiation of the mother, and (*c*) intrauterine infection with a virus or the parasite toxoplasma.

Antibiotics in Pediatrics

Progress in development of antibiotics has been so great and so well reported that only general principles will be reviewed. With the advent of each new antibiotic and the claims made for it, the treatment of acute and chronic infections seems at first to have become more complicated and confusing, although it is quite clear that treatment is far more effective. Many tables have been published listing the variety of pathogenic organisms with the antibiotics most likely to be effective against them. However, the usefulness of such tables depends entirely on accurate determination of the specific organism causing the illness and its antibiotic sensitivity spectrum.

Vigorous effort should be made to establish the etiologic diagnosis before therapy is begun. Therapy need not be delayed until the cultures are reported if all available sources for the organisms have first been cultured and smears examined.

In most small hospitals bacteriology is the poorest part of the laboratory services, although the type of bacteriological work that is required for good therapy is not complicated, time consuming, nor expensive. Sensitivity determinations using commercially available disks which have been impregnated with an antibiotic are easily done, inexpensive and, although far from infallible, have been shown to give needed information for effective treatment (9).

Effectiveness of treatment should be checked bacteriologically during the course of therapy. In treating severe or chronic infections, the original organism may be replaced by one that is resistant to the antibiotic being used, and a change of therapy would be indicated if this change can be recognized (10, 11, 12).

It is a pity that one of the by-products of the very great usefulness and efficiency of all these drugs has been a deterioration in the interest in exact bacteriological studies and a greater dependence upon blindly pre-

scribed therapy, even though it must be admitted that such therapy is immensly more effective than what we had a few years ago.

<center>TUBERCULOSIS</center>

Development of chemotherapeutic and antibiotic agents for the treatment of tuberculosis, although promising, is not nearly as satisfactory as antibiotic treatment of pyogenic infections. Nevertheless, progress has been made, which we need to review only as it affects children. Until recently, tuberculous meningitis was almost inevitably fatal within a month and miliary tuberculosis was almost as bad. The fact that we now obtain a considerable survival in tuberculous meningitis for months indicates, certainly without the necessity of control studies, that we have an agent of considerable effectiveness. Although results are by no means satisfactory even if life is saved, there appears to have emerged from the many studies of the last few years some definite principles of therapy.

Three major forms of childhood tuberculosis are susceptible to antibiotic and chemotherapeutic measures. These are in order of satisfactory responses: miliary tuberculosis, tuberculous meningitis, and progressive primary tuberculosis of the lung (13, 14).

A generally accepted treatment is 1 gm. streptomycin a day intramuscularly, para-amino-salacylic acid 0.5 gm. per kg. per day up to 12 gm. per day or 2-amino-5-sulfanilylthiazole (Promizole) starting at 0.5 gm. a day and increasing until a blood level of 1 to 3 mg. per cent is maintained (13). A recent report by the Public Health Service (78), utilizing the clinical facilities of several leading children's institutions indicates that a more effective dose of streptomycin is 50 mg./kg./day.

Intrathecal streptomycin is used in most clinics and is the series reported with the highest cure rate for an American series (13). However, this form of treatment results in severe reactions and probably increases the amount of eighth nerve damage.

What knowledge we have of pathogenesis of meningitis and of the mode of action of antibiotics poorly supports the logic of intrathecal treatment, and past experiences with intrathecal treatment of pyogenic meningitis by a series of antibiotics adds doubt to the need of such a mode of treatment. However, we could find only two reports with rather small numbers of cases in which the average American remission rate was achieved without resorting to intrathecal streptomycin (15, 16).

Streptomycin may be used for short periods of time to cover surgical procedures and for the short term treatment of draining sinuses. It seems not effective enough to be used in the long term treatment of tuberculous lymphadenitis, the standard accepted treatment for this disorder being surgical removal (17). Endobronchial tuberculosis, suspected when evidences of atelectasis develop or when lobar or segmental involvement is observed by x-ray, responds poorly to streptomycin therapy (13). Several studies in the last few years (18, 19, 20) indicate the high frequency of bronchiectatic

lessions following endobronchial tuberculosis with atelectasis, except where the upper lobes are involved. Because of this then, in certain selected cases many think it wise to remove the tuberculous granulation tissue causing the obstruction through a bronchoscope. However, we believe data do not, with certainty, support such treatment.

Although the antituberculous activity of isoniazid has been demonstrated it has not been under investigation long enough in pediatric practice to determine the best clinical regimens. Its use alone should not be depended upon.

POLIOMYELITIS

The advances in studies of poliomyelitis are exciting and give much hope. The changing age incidence of poliomyelitis is very striking and it is a long time since the old name "Infantile Paralysis" was at all appropriate. It is apparent from studies of the presence of immune bodies made in certain foreign countries, particularly in Egypt (21) as well as in this country, that economically advanced countries are beginning to pay a severe price for their better hygiene, in that infection with the virus of poliomyelitis and the development of natural immunity seems to be postponed to a later age when the risk of paralytic consequences of such infection is greater. In Egypt a far higher per cent of two year old children have circulating antibodies than in our own country, and the term "Infantile Paralysis" is still applicable to the disease as it occurs there. It seems that better hygiene forces us to be more dependent upon the development of some form of artificial active immunity. Steps towards the accomplishment of this are promising.

Probably the greatest single step toward some effective means of producing immunity was the development by Enders of tissue culture techniques (22) which have made it practical on a much greater scale to detect the virus and to measure it quantitatively and to measure the development of antibodies to it. Along with this there has been a painstaking survey and classification of all available strains of virus (23). These fall into three artificially separate groups: the Lansing, Brunhilde, and Leon strains. These studies furnish a practical basis for the development of a vaccine.

The introduction of temporary passive immunity by gamma globulin (24) has been of great interest, but it does not seem possible that satisfactory protection of our population can ever be brought about by its use. The most useful part that gamma gobulin will play may be in producing temporary passive immunity while active immunity is being established. At the moment we are going through a most distressing period during which we have only this agent with considerable evidence that it may prevent poliomyelitis at least for a few weeks, but in such short supply that its fair distribution creates an administrative problem impossible satisfactorily to solve.

Studies in monkeys and a few human beings indicate that active immunity is very likely to be a practical accomplishment in the near future, and this year a few human studies are being undertaken on a small scale.

Happily, some studies are being carried out seeking on antiviral chemo-

therapeutic agent in spite of the predominant interest in the techniques for prevention (25). Although little progress seems to have been made to the discovery of any practical agent, very basic studies are being made of virus and cellular metabolism which seem of great importance. It is apparent that although we have been able to prevent diptheria and whooping cough for years, that direct therapeutic procedures are still necessary.

RENAL PHYSIOLOGY

Premature infants show no limitation in their ability to dilute their urine following water ingestion and, per milliosmol of urinary solute, they can excrete as much as 20 ml. of water, which is the same as the adult (26, 27, 28). However, during the osmotic diuresis of forced NaCl ingestion, the premature infant excretes a larger volume of water per unit load than the adult and at similar levels of plasma osmolarity, the premature excretes an osmotic load approximately one-third that of an adult. This latter is in part due to the lowered glomerular filtration rate per unit of surface observed in the premature.

Observations of the response of the premature to infusions of bicarbonate (29) indicate that the acidosis of the "healthy" premature infant is not a result of immaturity of kidney function involving a lower maximum rate of tubular reabsorption of bicarbonate, but instead attributable to extra-renal factors.

Potassium tubular excretion readily occurs in premature infants, and the clinical implication is that immaturity of kidney function in the premature imposes no additional limitation on the rate at which potassium may be given in order to correct situations of potassium deficiency.

Studies of experimental and clinical dehydration of infants (30) showed an expected fall of glomerular filtration rate, with resultant conservation of water and electrolytes. This conservation of sodium and chloride occurred in spite of plasma hyperosmolarity.

Withholding of fluids in the immediate neonatal period (31) (up to four days of age) caused an elevation of serum sodium and chloride. Comparison of premature infants with those of full gestation revealed similar urine osmolarity, although premature infants excreted proportionately larger quantities of electrolytes and water. With onset of water ingestion, fluid retention occurred in all groups.

Further determinations of body water in various age groups (32) (utilizing the deuterium oxide dilution and the antipyrine method) showed values of body water, calculated as percentage of body weight, of 72 to 83 per cent in the neonatal period, with a fall during the first 6 months of life, and values of 53 to 63 per cent between ages of 6 months and 11 years of life.

NEPHROSIS

We still do not know the cause of "nephrosis" nor how to treat it effectively. The past few years have seen hormone therapy become dominant in

the many therapeutic adventures undertaken. Studies of current literature by this reviewer suggest that a more lenient program of therapy is the desired aim of the physician treating occasional or small numbers of these patients, rather than rigid programs with untasteful diets and frequent prolonged periods of hospitalization. Since no program is specifically effective or shows evidence of doing more than give symptomatic relief of edema, primary attention should be given to comfort and happiness of the patient.

One of the more thought-provoking approaches to understanding of pathogenesis has resulted from studies of an antigen-antibody phenomena in this disease (33, 34). It has been shown that autoantibodies to human kiney can be demonstrated in the blood stream of these patients. As values of antibody are low initially in the nephrotic syndrome, and later rise, it is theorized that the kidneys absorb and fix all the available antibody but that after saturation occurs, the presence of antibodies in the blood stream may be demonstrated.

Serum complement, which is essential in humoral antigen-antibody reactions, is low in nephrosis. However, in a day or two prior to occurrence of diuresis and remission the serum complement becomes elevated to normal levels. It is further shown that serum complement levels may be used for following nephrotic patients in remission, as a fall of serum complement preceded by several days an exacerbation of the illness.

The opportune time of attempted induction of diuresis is controversial. At present, adrenocorticotrophin and cortisone administration offer the most effective means of obtaining a diuresis in a large percentage of patients, both with nephrosis and with the nephrotic state of chronic glomerulotubular nephritis. Diuresis, but not cure, occurs in approximately 80 per cent of such patients given a course of either hormone (35). A failure for diuresis to appear during one course of hormone administration does not preclude a subsequent lack of diuresis following a repetition of therapy.

A newer agent for increasing the oncotic pressure of plasma is the complex polysaccharide, dextran, which when given by infusion has been shown to produce an immediate water diuresis in most cases (36, 37). The preparation may prove to be a clinically potent agent for obtaining a water diuresis.

Retrolental Fibroplasia

This very important and tragic disease of the newborn seems almost certainly a new one, definitely on the increase, and is rapidly becoming of major importance statistically as a cause of blindness. It appears to be a clinical entity with some scanty evidence that it may be part of a systemic disease (38).

The condition occurs primarily in premature infants, more frequently in the smaller ones under three and one-half pounds. It is a disease of the retina and vitreous which begins to be detectable soon after birth when a transient vitreous haze or opacities may be seen (39). Venous engorgement occurs, usually between the fourth and sixth weeks of life, to be followed by

hemorrhage, exudate, retinal separation with proliferation of new blood vessels followed by scarring which pulls the retina into a disorganized mass behind the lens.

The disease progresses irregularly and has been observed to regress spontaneously (40). The amount of residual damage, therefore, is variable. With more careful inspection of the eyes of all newborn, and particularly premature infants, it seems to some that no very sharp distinction between variations in normal and that of disease can be made at the very beginning. It is possible, therefore, that this condition may be far more widespread and more benign than was first thought.

There is still some question that the beginning of the disease may occur prenatally, and if so, this is, of course, of extreme importance in regard to speculation as to etiology. It is conceivable that it is attributable to infection though, at the moment, there is little support for this concept.

Some have felt that this is not a new disease and that its present frequency is simply the result of a higher per cent of salvage of smaller premature infants. Although a little support for this may be derived from mass statistics which show somewhat greater survival rate of premature babies during the past 12 years, which is the time this disease has been recognized, nevertheless, experience in certain very well run clinics where great interest in premature babies has been shown for many years with elaborate and thorough follow-up of almost all patients makes us feel that this is definitely a new disease and not a belated discovery of an old one.

Considering that it is a disease with postnatal etiology, many have speculated as to what is new in the last decade in the care of premature infants that has caused this terrible thing to appear. Blame has been put, by speculation mostly, on greater use of cow's milk (thus higher protein and mineral intake), on more widespread use of incubators, on the use of antibiotics, and higher dosage of vitamins, and on the greater use of oxygen. One by one, most of these factors seem to have been eliminated, though not conclusively. At the moment, the most promising lead is that in fact the disease may be attributable to the greater use of higher concentrations of oxygen in incubators or the intermittent use of such oxygen levels. An extensive study of this one factor is at present being made in a combined co-operative study by many clinics, and an answer may be obtained within a year.

There is no good evidence that any therapeutic procedure has prevented the advance of this disease. As might be expected, the use of ACTH and cortisone was hopefully tried, but this seems certainly unsuccessful now. An excellent summary with complete references is to be found in the report of the proceedings of the Retrolental Fibroplasia Conference sponsored by the M & R Laboratories and held at the Bellevue Medical Center in New York City on April 28, 1951.

PULMONARY HYALINE MEMBRANE

The term "pulmonary membrane disease" is one of recent development, and it is now used rather commonly and, in the opinion of this reviewer,

quite unjustifiably as if it were a disease entity and adequately explained otherwise obscure deaths in new born infants (41). Its use this way is reminiscent of the term "thymus disease" which was used, and still is to a certain extent, as an explanation of infant death that the medical profession does not clearly understand, but for which they got some backing from superficial interpretation of pathological morphology.

Pulmonary "hyaline membrane" has been the term used for an eosinophilic staining material found lining the alveoli or alveolar ducts in certain newborn infants who die with obstructive dyspnea.

This morphological finding in the lung has been found after death in many situations where severe terminal dyspnea has occurred with the presence of an eosinophilic fluid material in the respiratory tract. It was described many years ago in the 1918 "flu" epidemic (42), and it has been produced by simple mechanical methods experimentally in dead lungs (43). There is no question, however, that the finding is mysteriously common in certain premature infants who die from causes not adequately understood. It is clear that we do not understand what this exudate is chemically nor why it occurs as commonly as it does in these small infants, but it is not at all clear that it itself is the cause of dyspnea or death. Clinical observation of many premature infants shows a state of dyspnea which has never been adequately explained unless we resort to such acceptance of our ignorance as a statement that the babies are too immature to live, which is clearly enough true.

It is clear that this "membrane" could be in part attributable to the aspiration of amniotic fluid. It could also result from an exudate of the infant's own plasma into the bronchial tree, and the possibility of this occurring is made a little greater when one thinks of the general immaturity of the autonomic nervous system and the vascular system. The problems of the extent of intra-uterine respiration, its effectiveness in causing tidal flow, and its aggravation by anoxia has been reconsidered in possible relation to the hyaline membranes without any definite conclusions being made. It must be kept in mind that the only opportunity for study of this histological finding is in children who have died. We have no idea whether similar occurrences might be found in other babies who survive.

Some observers have held that the membrane is more likely to be found in infants who have suffered some intra-uterine asphyxia and have had violent intra-uterine respiratory movements. This is certainly not established.

Some observers feel this entity occurs more frequently in children born of diabetics and in the premature infants that are the products of Caesarean section. In the latter it would not be difficult to correlate increased amount of amniotic fluid in the pulmonary tree with the type of delivery. It is more difficult to do this with premature infants who are born before the greatest amount of respiratory activity takes place and when amniotic fluid is relatively small in amount.

This reviewer could find nothing in the literature reporting correlation of laboratory and clinical findings in these infants. Many observers state

these infants suffer from cyanosis and that they can make the clinical diagnosis on this basis. It would seem if this were so then every infant where this would be suspected might well be in a state of respiratory acidosis with increased tension of CO_2 in the plasma. No one seems to have made this observation, though from our own unpublished data it appears that most infants born of diabetic mothers do have a greater CO_2 tension at birth, indicating a state of respiratory acidosis.

In a conference held by a group of physicians to discuss this disease (44) someone brightly referred to the hyaline membrane as an "eosinophilic herring." Although it may well turn out that this finding is more than an incidental histological detail or almost an artifact, it must be kept in mind that at the moment we do not know its chemical content and its finding should not be used as a ready and satisfactory explanation of death.

CHRONIC EOSINOPHILIA WITH HEPATOMEGALY

In 1949, Zuelzer & Apt (45) described eight cases in early childhood of eosinophilia associated with hepatomegaly and granulomatous lesions in the liver demonstrated by biopsy in seven cases and post-mortem examination in the eighth. They suggested an allergic-hyperergic reaction as the basis for these lesions although they were unable to demonstrate a source of antigen, such as *Ascaris* infestation, either clinically or pathologically. The disease usually appears to run a chronic and benign course.

Reports of similar cases had been made prior to 1949. Perlingiero & György (46) reported a case in a two year old Negro child who had a large liver and eosinophilia and in whom a liver biopsy showed typical focal necrotic lesions. This child vomited a single *Ascaris* during the course of his illness. Since 1949, there have been other reports (47 to 51) and it is possible, if not probable, that these represent the same entity described by Zuelzer.

Clinically, the reported cases have occurred in young children from one to four years of age. There may or may not be an acute phase of illness with fever, malaise, painful extremities and joints, urticaria, and pulmonary manifestations such as cough or asthmatic-like symptoms. Hepatomegaly is always present. Laboratory examination shows a leukocytosis up to 50,000 with an eosinophilia up to 80 per cent. The bone marrow also shows an eosinophilia. There is an elevated total serum protein with an increase in the globulin fraction. The liver is studded with small grayish-white lesions which show focal areas of necrosis with eosinophilic infiltrates and multinucleated giant cells microscopically. In five cases thus far a roundworm larva, either *Ascaris lumbricoides* or *Toxocara canis*, has been demonstrated in these lesions. The difficulty of demonstrating the larvae has been stressed by those who have succeeded in doing so. Serial sections through given areas have been done in order to find a single larva.

The majority of authors have agreed that the most likely basis for the picture seen is that suggested by Zuelzer, with the roundworm larva serving as a localized antigen. There is no therapy recommended at the present tim unless roundworms are present.

Beaver *et al.* (52) were able to produce similar focal necrotic areas in mice livers by feeding eggs of *Toxocara canis* to the mice. A widespread visceral dissemination of the larvae occurred by 11 days, and 2 months later both active and dead encapsulated larvae were still present.

Pathologically the liver lesions are similar to those in the lungs in Loeffler's syndrome, and it has been suggested that the latter entity has the same basis with the larvae being trapped in the lungs.

Megaloblastic Anemia of Infancy

In 1946 Zuelzer & Ogden (53) reported on a clinical entity in infants associated with a megaloblastic anemia which was characterized by a dysplasia and dysfunction of bone marrow developing from the lack of a specific hemopoietic factor. In most instances the anemia was normochromic and macrocytic in type, and in about a third of the babies clinical scurvy was also present. Free gastric hydrochloric acid was not present in some instances initially. The bone marrow in these infants was megaloblastic in nature and in addition showed changes in developing granulocytes which are like those present in pernicious anemia.

Since 1946 the work of May and his associates (54 to 58) on the experimental production of megaloblastic anemia in monkeys has tended to substantiate the initial concept of megaloblastic anemia in infancy as a deficiency disease. On a cow's milk diet deficient in ascorbic acid monkeys usually developed clinical scurvy initially, followed by megaloblastosis within a matter of weeks. Infection was shown to be an important additional factor in the development of the disease as monkeys with abscesses developed megaloblastosis even when kept on adequate diets. Vitamin B_{12} neither prevented megaloblastosis nor cured it once it was present. Folic acid and even more particularly folinic acid were quite specific in reversing the marrow picture to normal, and Vitamin C also caused the bone marrow to return to normal but over a longer period than with other therapy. Changes in the bone marrow appeared as little as two hours after therapy was begun, and peak reticulocyte responses occurred within four to five days following the onset of therapy.

Since 1946, clinical reports of megaloblastosis in infants have been rare. However, application of the experimental findings of May *et al.* to cases of megaloblastosis in infants has shown the effectiveness of folic acid and especially folinic acid, and most infants have not needed sustained therapy in the presence of an adequate diet and in the absence of infection.

Erythroblastosis Fetalis

Erythroblastosis fetalis has occupied an enormous amount of attention in obstetric and pediatric circles in the last 20 years and has been subject to a great deal of excellent research as well as rather wild speculation. Few diseases have been subject to more dogmatic reports as to etiology and treatment. There are still many holes in our knowledge of this disease. It seems to this reviewer rather unfortunate that such dogmatism by several

writers has existed and terminology has been allowed to develop which is unsound. For instance, the use of the term "kernicterus" as identical with general brain damage resulting from this disease seems unfortunate, as surely kernicterus is not limited only to this disease, and the clinical symptomatology is not at all closely related to the pathological findings which justify the term "kernicterus." It is our opinion that the term should be reserved for a pathological and not a clinical description of what is found at post-mortem examination.

Although the pathogenesis of the hemolytic process in erythroblastosis fetalis is fairly well understood at present, there is still no adequate explanation for the appearance of signs of central nervous system damage. Whether it depends on the presence of bilirubin in certain nuclear centers of the brain or whether there is some other breakdown product of red blood cell destruction that causes the damage is not known. In the past five years there has been some evidence that this serious complication has been lessened by the use of exchange transfusion done shortly after birth. Mollison & Walker in England (59) were able to carry out the first controlled series of 477 cases where alternate infants with a diagnosis of erythroblastosis fetalis were given exchange transfusions. The remaining babies received at least one small transfusion at birth and then received more blood via small transfusion as was needed. A preliminary report showed a significant decrease in the incidence of kernicterus in those infants receiving exchange transfusions.

A more recent association between the level of bilirubin in the blood and the development of kernicterus has been clarified by Hsia *et al.* (60). When the total bilirubin level exceeded 15 mg. per cent, there was an 18 per cent incidence of kernicterus, and when it exceeded 30 mg. per cent, the incidence rose to 50 per cent. They have proposed doing serial bilirubin levels and attempting, by the use of exchange transfuion, to keep the bilirubin level below 20 mg. per cent.

Advances in Treatment of Congenital Defects of the Heart

In few directions have advances in the Pediatric Age been so exciting or satisfying as in the development of procedures for correcting congenital abnormalities of the heart and great vessels. In rapid succession new surgical techniques have appeared, soon to be improved upon, and their mortality so reduced, permitting us to give hope to many despondent parents.

Since Gross (61) successfully ligated a patent ductus arteriosus in 1939, surgical techniques have been developed for the relief of numerous other cardiovascular lesions. When it became apparent that a significant number of ducti recanalized after simple ligation, division (62) of the ductus was undertaken. This technique of repairing an arterial structure which had been severed, opened the way for a number of plastic vascular procedures. The relief of coarctation of the aorta was accomplished in 1945, when Crafoord (63) removed the constricted portion of this artery and reestablished aortic continuity by anastomosis of the free ends of the vessel. For those patients

in whom the site of coarctation was such that primary anastomosis was impossible, Gross *et al.* (64) contributed the use of preserved homologous aortic grafts to bridge the gap. The same author (65) relieved the tracheal compression caused by a double aortic arch encompassing the trachea and esophagus by dividing the anterior arch.

The first steps in the surgical treatment of cyanotic congenital heart defects were reported by Blalock & Taussig (66) in 1945. Realizing that the most important disturbance in tetralogy of Fallot was the insufficient passage of blood through the lungs, they set out to shunt back to the pulmonary arteries some of the anoxemic blood which left the right ventricle through the overriding aorta, thus by-passing the lungs. The subclavian artery branching from the innominate was found to be the most suitable for the creation of this shunt. Later a direct communication between the aorta and pulmonary artery was made possible through the development of an ingenious clamp by Potts, Smith & Gibson (67).

In pulmonary valvular stenosis without an interventricular septal defect, the creation of an aorticopulmonary shunt is detrimental. Realizing this, Brock (68) used a valvulotome on the stenosed pulmonary valve, approaching it through the right ventricle. With the obstruction thus removed, the work of the right ventricle is greatly relieved. The direct attack was later extended to the infundibular pulmonary stenoses by Brock (69) using a backward cutting punch and by Glover, Bailey & O'Neill (70) using a small, sharp bone rongeur; both the pulmonary valvulotomy and infundibulectomy have also been used in the treatment of tetralogy of Fallot. While they are certainly a more physiological approach to the problem they do carry higher mortality rates than the shunting operations.

Among the less common lesions recently corrected surgically is the septal defect between the ascending aorta and common pulmonary artery. Gross (71) treated this condition by simple ligation, while Scott & Sabiston (72) used division. Muller (73) corrected an anomalous pulmonary venous return by transposing the common left pulmonary vein from the right auricle, into which it drained, to the left auricular appendage.

A number of different procedures have been tried for the closure of interauricular septal defects without very great success. Swan (74) attempted occlusion of the auricular opening through the invagination of one or both auricular appendages. To permit a direct approach to the closure of an auricular defect, Dennis *et al.* (75) used a mechanical heart-lung machine to divert venous return from the heart, unfortunately unsuccessfully. Gross *et al.* (76) have approached the problem by using a rubber "well" which opens into the auricle at its base and is sufficiently high to prevent the loss of blood rising in it under auricular pressure. By this device the surgeon is able to palpate the defect within the auricle and repair it in a careful and unhurried manner. Lewis & Taufic (77) have used hypothermia to permit direct exposure of an auricular defect while the venous return to the heart was temporarily occluded. All cardiac flow was obliterated for five and

one-half minutes during which time the defect was visualized and closed under direct vision with complete recovery of the patient following surgery. It seems possible that hypothermia will open up an entirely new approach to intracardic plastic surgery.

LITERATUTE CITED

1. Statistics of Metropolitan Life Insurance Co. (1948–49)
2. Rosenfield, A. B., *Minnesota Med.*, **35**, 424 (1952)
3. Dietrich, H. F., Wheatley, G. M., and Brooks, G. L., *Pediatrics*, **8**, 426 (1951)
4. Vital Statistics Reports of the Bureau of the Census (1945)
5. Miller, H. C., Stern, C., Yannet, H., and Warkany, J., *Pediatrics*, **5**, 320 (1950)
6. Gregg, N. M., *Trans. Ophthalmol. Soc. Australia*, **3**, 35 (1942)
7. Plummer, G., *Pediatrics*, **10**, 687 (1952)
8. Warkany, J., in *Advances in Pediatrics*, **II**, 1 (Levine, S. Z., Ed., The Year Book Publishers, Inc., Chicago, Ill. 1947)
9. Spaulding, E. H., *Pediatrics*, **8**, 406–12 (1951)
10. Garrard, S. D., Rochmond, J. E., and Hirsch, M. M., *Pediatrics*, **8**, 482 (1951)
11. Harris, H. J., *J. Am. Med. Assoc.*, **142**, 161 (1950); Williams, B., Jr., *Am. Practitioner and Dig. Treatment*, **1**, 897 (1950); Finland, M., *Bull. N. Y. Acad. Med.*, **27**, 199 (1951); McVay, L. V., Jr., and Sprunt, D. H., *Proc. Soc. Exptl. Biol. Med.*, **78**, 759 (1951)
12. Woods, J. W., Manning, I. H., Jr., and Patterson, C. N., *J. Am. Med. Assoc.*, **145**, 207 (1951); Gausewitz, P. L., Jones, F. S., and Worley, G., Jr., *Am. J. Clin. Pathol.*, **21**, 41 (1951); Brown, C., Jr., Propp, S., Guest, C. M., Beebe, R. T., and Early, L., *J. Am. Med. Assoc.*, **152**, 206 (1953)
13. Lincoln, E. M., and Wilking, V. M., *Am. J. Diseases Children*, **82**, 655–65 (1951)
14. Levine, M. I., *Pediatrics*, **9**, 791–800 (1952); Levine, M. I., *Am. J. Diseases Children*, **68**, 385 (1944); Meyers, J. A., and McKinley, C. A., Eds., *The Chest and the Heart* (Charles C Thomas, Publisher, Springfield, Ill., 1948)
15. Levinson, A., *Am. J. Diseases Children*, **77**, 709 (1949)
16. Perry, T. L., *J. Pediat.*, **40**, 687 (1952)
17. Sevenson, O., and Small, W. T., *Pediatrics*, **10**, 131 (1952)
18. Jones, E. M., Peck, W. M., and Willis, H. A., *Am. J. Diseases Children*, **72**, 296 (1946)
19. Veeneklaas, G. M. H., *Am. J. Diseases Children.*, **83**, 271 (1952)
20. Hardy, J. B., Proctor, D. F., and Tuner, J. A., *J. Pediat.*, **41**, 740 (1952)
21. Paul, J. R., Melnick, J. L., Barrett, V. H., and Goldblum, N., *Am. J. Hyg.*, **55**, 402 (1952)
22. Ender, J. F., *J. Immunol.*, **69**, 639–43 (1952)
23. The Committee on Typing of the National Foundation for Infantile Paralysis *Am. J. Hyg.*, **54**, 191 (1951)
24. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., and Stokes, J., Jr., *J. Am. Med. Assoc.*, **151**, 1272 (1953)
25. Francis, T., Jr., *Mich. Alumni Quart. Rev.* (February, 1953)
26. Barnett, H. L., Vesterdal, J., McNamara, H., and Lauson, H., *Am. J. Diseases Children*, **84**, 481 (1952)
27. Calcagno, P., Rubin, M. I., and Weintraub, D. H., *Am. J. Diseases Children*, **86**, No. 3, 344 (1953)

28. Barnett, H., Vesterdal, J., McNamara, H., and Lauson, H., *J. Clin. Invest.*, **31,** 12, 1069 (1952)
29. Tudvad, F., McNamara, H., and Barnett, H. L., *Am. J. Diseases Children*, **86,** No. 5, 612 (1953)
30. Calcagno, R., and Weintraub, D. H., *Am. J. Diseases Children*, **80,** 514 (1950)
31. Hansen, J. D. L., and Smith, C. A., *Am. J. Diseases Children*, **84,** 4, 477 (1952)
32. Friis-Hansen, B. J., Holliday, M., and Stapleton, T., *Am. J. Diseases Children*, **80,** 3, 515 (1950)
33. *Third Annual Conference on the Nephrotic Syndrome* (Metcoff, J., Ed., The National Nephrosis Foundation, Inc., New York, N. Y., 70 pp., 1953)
34. Lange, K., Slobody, L., and Strang, H., *Am. J. Diseases Children*, **86,** 478 (1953)
35. Barnett, H., Forman, C., and Lauson, H., *Advances in Pediatrics*, **5,** 53–118 (The Year Book Publishers, Inc., Chicago, Ill., 273 pp., 1952)
36. James, J. A., Conway, D. J., Gordillo, G., and Metcoff, J., *Soc. Pediat. Research.*, *23rd Annual Meeting* (1953)
37. Aldrich, R. A., Perley, A., and Hutchins, T., *Soc. Pediat Research*, *23rd Annual Meeting* (1953)
38. *Proc. Retrolental Fibroplasia Conference* (Bellevue Medical Center, New York, N.Y., April 28, 1951)
39. Terry, T. L., *Am. J. Ophthalmol.*, **25,** 203 (1942)
40. Owens, W. C., and Owens, E. U., *Am. J. Ophthalmol.*, **32,** 1–12, 1631–37 (1949)
41. Miller, H. C., Behrle, F. C., and Gibson, D. M., *Pediatrics*, **7,** (5), 611–15 (1951)
42. Wolbach, S. B., *Bull. Johns Hopkins Hosp.*, **30,** 104 (1919)
43. Farber, S., and Wilson, J. L., *Arch Pathol.*, **14,** 437, 450 (1932)
44. *The Fifth M&R Pediat. Research Conf.* (St. Christopher's Hospital for Chlidren, Philadelphia, Penna., April 16, 1952)
45. Zuelzer, W. W., and Apt, L., *Am. J. Diseases Children*, **78,** 153 (1949)
46. Perlingiero, P. G., and György, P., *Am. J. Diseases Children*, **83,** 649 (1952)
47. Bass, M. H., *Am. J. Diseases Children*, **62,** 68 (1941)
48. Behrer, M. R., *J. Pediat.*, **38,** 635 (1951)
49. Mercer, R. D., Lund, J. Z., Bloomfield, R. A., and Caldwell, F. E., *Am. J. Diseases Children* **80,** 46 (1950)
50. Milburn, C. L., and Ernst, K. F., *Pediatrics*, **11,** 358 (1953)
51. Silver, H. K., Henderson, P., and Contopoulos, A., *Am. J. Diseases Children*, **83,** 649 (1952)
52. Beaver, P. C., Snyder, C. H., Carrera, G. M., Dent, J. H., and Lafferty, J. W., *Pediatrics*, **9,** 7 (1952)
53. Zuelzer, W. W., and Ogden, F., *Am. J. Diseases Children*, **71,** 211 (1946)
54. May, C. D., Nelson, E. N., Lowe, C. U., and Salmon, R. J., *Am. J. Diseases Children*, **80,** 191 (1950)
55. May, C. D., Sundberg, R. D., Schaar, F., Lowe, C. U., and Salmon, R. J., *Am. J. Diseases Children*, **82,** 282 (1951)
56. May, C. D., Hamilton, A., and Stewart, C. T., *Blood*, **7,** 978 (1952)
57. May, C. D., Stewart, C. T., Hamilton, A., and Salmon, R. J., *Am. J. Diseases Children* **84,** 718 (1952)
58. Sundberg, R. D., Schaar, F., and May, C. D., *Blood*, **7,** 1143 (1952)
59. Mollison, P. L., and Walker, W., *Lancet*, **I,** 429 (1952)
60. Hsia, D. Y., Allen, F., Gellis, S., and Diamond, L., *New Engl. J. Med.*, **247,** 668 (1952)

61. Gross, R. E., *New Engl. J. Med.*, **220**, 510 (1939)

62. Gross, R. E., *J. Thoracic Surg.*, **16**, 314 (1947)

63. Crafoord, C., and Nylin, G., *J. Thoracic Surg.*, **14**, 347 (1945)

64. Gross, R. E., Gill, A. H., Jr., and Peirce, E. D., II., *Surg. Gynecol. Obstet*, **88**, 689 (1949)

65. Gross, R. E., *New Engl. J. Med.*, **233**,586 (1945)

66. Blalock, A., and Taussig, H. B., *J. Am. Med. Assoc.*, **128**, 189 (1945)

67. Potts, W. J., Smith, S., and Gibson, S., *J. Am. Med. Assoc.*, **132**, 627 (1946)

68. Brock, R. C., *Brit. Med. J.*, **I**, 1121 (1948)

69. Brock, R. C., *Brit. Med. J.*, **II**, 399 (1949)

70. Glover, R. P., Bailey, C. P., and O'Neill, T. J. E., *J. Am. Med. Assoc.*, **144**, 1049 (1950)

71. Gross, R. E., *Circulation*, **5**, 858 (1952)

72. Scott, H. W., Jr., and Sabiston, D. C., Jr., *J. Thoracic Surg.*, **25**, 26 (1953)

73. Muller, W. H., Jr., *Ann. Surg.*, **134**, 683 (1951)

74. Swan, J., *J. Am. Med. Assoc.*, **151**,792 (1953)

75. Dennis, C., Spring, D. C., Nelson, G. E., Karlson, D. E., Nelson, R. M., Thomas, J. V., Eder, W. P., and Varco, R. L., *Ann. Surg.*, **134**, 709 (1951)

76. Gross, R. E., Watkins, E., Jr., Pomeranz, A. A., and Goldsmith, E. I., *Surg. Gynecol. Obstet.*, **96**, 1 (1953)

77. Lewis, F. J., and Taufic, M., *Surgery*, **33**, 52 (1953)

78. Public Health Service Cooperative Investigation Chemotherapy of Miliary Tuberculosis and Tuberculous Meningitis, *Pediatrics*, **12**, 38 (1953)

DENTISTRY[1]

By Henry M. Leicester

*Department of Physiological Sciences, College of Physicians and Surgeons of
San Francisco, A School of Dentistry, San Francisco, California*

The teeth are unique bodily structures, both in their anatomical location which renders them easy of access to external effects, and in their chemical nature. They are not capable of the immediate response to attack which is found in the soft tissues, and by their predominantly inorganic composition they can undergo chemical and physicochemical changes which are not observed even in bone, the tissue which most closely resembles them.

There are two distinct phases in the life of teeth; the developmental period during which they are extremely responsive to systemic and metabolic changes, and the period after eruption, during which their response to bodily changes is very limited. The biochemical nature of the teeth has been reviewed extensively recently (1, 2) and need not be discussed again here. Little work on the effects of vitamin or mineral deficiencies or of hormonal imbalances on the teeth is very recent, and such work has also been covered in the reviews. This review will therefore be confined to the newer discoveries on the effects of radiation on the developing tooth, and on the etiology and prevention of dental caries.

Radiation.—Interest in the effects of radiation on tooth formation has naturally grown in recent years. It has long been known that clinical exposure to x-rays in humans can result in disturbed tooth development. Typical of such disturbances are those reported by Bruce & Stafne (3) who cite five cases of irradiation therapy in infancy which resulted in disturbed formation and eruption of teeth. Recent studies in animals have given a clearer picture of such effects than can be obtained by clinical studies.

Medak, Schour, & Klauber (4) have shown that single exposures of 3000 to 4000 r slow or prevent eruption of rat incisors, and that this effect is direct and not mediated through the hypophesis. Burstone (5) found marked disturbance of enamel and dentin formation in mice at doses of 1500 to 5000 r when the area of the mandibular joint and molar teeth was irradiated directly. In agreement with earlier workers, he found the dentin forming cells to be more sensitive than those forming enamel. English & Tullis (6) found active enamel forming cells in swine given whole body irradiation above 400 r to be most sentitive, and Dale (7) observed the same relative sensitivity in rats with whole body irradiation up to 750 r. Medak *et al.* (8) made a careful histological study of rat incisors subjected to single doses of irradiation, and suggested that it was not the dentin forming cells themselves which suffered first, but the zone of intense proliferation, that of the pulpal tissue next to the dentin forming cells. Circulatory damage in this area could prevent prop-

[1] The survey of the literature for this paper was concluded July 15, 1953.

er dentin formation. This explanation is in line with the fact that the most rapidly devloping cells are usually most radiosensitive, and may explain the contradictory reports in the literature as to the relative sensitivity of enamel and dentin.

Burstone has shown that there is some danger to the teeth in the use of radioactive isotopes, since gold (9) and phosphorus (10) used as tracers may also damage developing teeth in mice. Kalnins (11) showed that in guinea pigs large doses of ascorbic acid protected both alveolar bone and developing dentin from damage by irradiation. When large doses of the vitamin were administered, osteoblasts were more radiosensitive than dentin forming cells; when small doses were given, the reverse was true.

Caries etiology.—There have been two recent extensive reviews on all phases of dental caries (12, 13). These cover the literature down to about 1950.

Two theories of the etiology of caries have been dominant in recent years. The older theory, that caries is attributable to fermentation of carbohydrates on the teeth with production of acid which dissolves the inorganic substance, has been challenged by supporters of the idea that an attack by proteolytic bacteria on the matrix of enamel and dentin is an important part of caries. Shaw (14) has reviewed the evidence for the acidogenic theory, and Frisbie (15) that for the proteolytic theory. It seems probable that both of these mechanisms are involved in any carious lesions, the predominating effect at any one time being attributable to the structure of the tooth itself and the availability of acidogenic or proteolytic bacteria at the site of the lesion. Many of the recent studies on caries etiology and prevention support this view, since they definitely implicate one or the other of these mechanisms.

As a result of much work on the bacteriology of caries, it is commonly assumed that *Lactobacillus acidophilus* is the chief causative agent. This view has always been disputed by some, and recent work has further implicated a number of other organisms. Even the significance of lactobacilli as an indicator of caries activity has been questioned by Boyd & co-workers (16, 17) and by Glass (18) who did not find a correlation between salivary lactobacillus counts and amount of caries. Davies (19) noted that the total amount, but not the type of lactobacilli, correlated with caries. Some of the discrepancies reported may be attributable to the fact that many other acidogenic organisms are present in the saliva, often in amounts greater than the lactobacilli themselves. In particular, acidogenic streptococci have been found to be up to four times as numerous as lactobacilli [Parsons, McCollum & Frobisher (20), Shiere, Georgi & Ireland (21), Fitzgerald (22)]. Harrison (23) suggested that lactobacilli were associated with initiation of caries in enamel, while streptococci were found in advanced caries of the dentin. Lammers (24) assumed a symbiosis between the two organisms. Hurst, Nuckolls & Frisbie (25) found that caries-like lesions could be produced in vitro by actinomycetes, and that these organisms were found in

carious lesions [Onisi & Nuckolls (26)]. Ennever, Robinson & Kitchin (27) suggested, however, that actinomycetes were not necessarily related to caries, but might form the structural frame of the dental plaque, the mucinous film under which caries often progresses.

In any event, while it is clear that the presence of glucose or sucrose in the mouth causes a sharp rise in acid production [Strålfors (28), Ericsson & Helström (29)], proteolytic bacteria are present and can digest protein under the proper conditions. There is little agreement as yet as to which oral proteolytic bacteria are involved in caries. Wakeman *et al.* (30) noted strongly proteolytic enterococci in carious lesions. Hartles & McLean (31) found *Clostridium welchii* which could produce acid from glucose and also hydrolyze chondroitin sulfuric acid. The latter action has been implicated in caries by Pincus (32) who found calcium sulfate in carious lesions, but not in sound teeth. Evans & Prophet (33, 34) showed that the collagenases of *C. welchii* and related organisms attacked the organic component of powdered, decalcified human dentin. Prophet & Atkinson (35) found that this disintegration did not occur in carious dentin *in vitro*, indicating that dentinal caries involves not merely a decalcification, but also a change in the nature of the organic matrix. Engel (36) made similar observations, though the work of Coolidge (37) did not confirm them. Burnett & Scherp (38) found that proteolytic organisms from carious lesions hydrolyzed protein only after the protein matrix had been exposed to acid attack.

Thus the bacteriology of caries is still confused, but it is growing clearer that lactobacilli are not the sole important factor. Whatever the organisms concerned may be, their nutritive requirements must be met if caries is to progress. Koser & Fisher (39) showed that all oral lactobacilli require nicotinic acid, pantothenic acid, and biotin for growth, and many require B_6, pteroyl glutamic acid, thiamine or riboflavin in addition. Koser, Fisher & Kauffman (40) found that when less than the optimal amounts of needed vitamins were supplied, acid production still occurred, but the pH of the medium was higher. Dreizen & Spies (41) found that the need for nicotinic acid, pantothenic acid, and biotin was shown by pure strains or mixtures of strains of lactobacilli, streptococci, staphylococci, and yeasts, while thiamin and riboflavin were also needed by some strains, They suggested that species and strain differences in B vitamin requirements might explain the variations noted in different individuals or in the same individual at different times in acid production in saliva. Dreizen, Reed & Spies (42) observed a close relation between the nicotinic acid content of saliva and caries activity, thus explaining the low caries rate in pellagrins. The same authors (43) showed that salivary mucin was a poor source of amino acids required by lactobacilli unless amylolytic or proteolytic enzymes were present to break it down. It is thus clear that the nutritional requirements of the oral bacteria are significant in the total caries picture.

The importance of carbohydrate in the human diet in producing caries is generally accepted, but recent studies have stressed the fact that the form of

the carbohydrate is significant. The studies of Stephan (44), Shafer (45). Orland (46), and Cartier, Cartier & Picard (47) show that starch is less cariogenic than sucrose or glucose. Even the form of the sugar is important, since Wynn *et al.* (48) and Granados, Glavind & Dam (49) showed that different diets which contained the same absolute amount of sugar differed greatly in the amount of caries they produced. Zepplin *et al.* (50) showed that in cotton rats a diet comparable to a normal American diet, and containing 17 per cent sucrose, was more cariogenic than a synthetic diet containing 67 per cent sucrose. Haldi *et al.* (51) showed that sugar in solution caused less caries than when it was given as a solid. Neuwirth & Summerson (52) and Calandra & Adams (53) indicated that the rate of production and oxidation of pyruvic and lactic acids under various conditions could partly account for these differences.

A variety of other factors in general diets seem related to caries production. Fluid rations in general are less cariogenic than are solid ones [Anderson *et al.* (54, 55)]. Constant, Phillips & Elvehjem (56) found that processed cereals produced more caries than whole grain cereals. McClure & Folk (57) showed that powdered skim milk which had been heated during evaporation was more cariogenic than that prepared at lower temperatures. The report of Nizel & Harris (58, 59) that foods grown in New England soil contain a factor aiding caries production which does not occur in similar foods grown in Texas requires further confirmation. It is known from the work of Sognnaes (60) and Shaw (61) that diets adequate in all known respects do not necessarily prevent caries.

A very significant finding has recently been reported by Sognnaes (62) who observed that a diet high in sugar for the mother during pregnancy seems to predispose the offspring to caries in later life when they receive a cariogenic diet, while if the maternal diet was low in sugar during pregnancy, the same cariogenic diet in later life will not produce caries in the offspring. This observation was made on animals, but studies of children born during World War II, when sugar was unavailable to the mothers, seem to confirm the observation for humans. Sognnaes (63) has noted this fact in Scandinavian children, and Bransby & Knowles (64) noted it in children from the Channel Islands.

This finding implies a change in tooth structure resulting from the low sugar maternal diets. Slight structural changes have been reported under these conditions by Hartles (65) and by Herrmann & Cremer (66), but the full significance of such changes is not yet clear. The theoretical and practical significance of the findings are great, however. It is obvious that much previous work in which the maternal diet was not considered will have to be reevaluated. It is also clear that this effect will have to be considered in planning diets during pregnancy.

From all the foregoing it is plain that the usual generalized picture of caries is far too simple, and that there are many details to be considered in any picture of caries etiology. It is probable that some of these represent

rather minor variables which when fitted into the complete picture will seem of slight importance, but in the present state of our knowledge they cannot be neglected.

Caries prevention.—The complexity of caries etiology might seem to make the problem of caries prevention very difficult. Actually, it is more likely to simplify it. Since it is now obvious that caries results from a number of closely interlinked processes, and since most of these processes themselves are made up of interlinked chain reactions, it is necessary to prevent only a relatively small number of key reactions to prevent the entire process. Up to now, most attention has been centered on the acid factor in caries etiology, and so it is not surprising that almost all the methods proposed for caries prevention involve the inhibition of some step in this process. This is no doubt a reason that no one method has yet been found to prevent caries completely. Substantial reductions can be obtained with methods now available, and when other factors involved in the carious lesion are better understood, complete caries prevention will probably follow.

The oldest method of caries prevention is the reduction of sugar intake. This has been and is being stressed intensively. It is very effective when properly applied, but for psychological reasons it is probably the most difficult method to use on a large scale. The other methods which have been developed are less open to this objection.

Most attention in recent years has been devoted to the use of fluorides for reduction of caries. These studies have established its efficacy beyond question. Topical application of 2 per cent sodium fluoride to the teeth of children results in a reduction of about 40 per cent in caries incidence [Knutson & Scholz (67)]. Almost all the original studies of this method were made on the teeth of children, but the observations have now been extended to the teeth of young adults, but with somewhat contradictory results. Klinkenberg & Bibby (68) noted a 44 per cent reduction in caries in adults aged 18 to 40 yrs., and Rickles (69) made a similar observation. On the other hand, Marshall-Day (70) and Kutler & Ireland (71) found little or no reduction. Further studies are required in this field.

Even more effective is the ingestion of 1 p.p.m. fluoride in the drinking water during tooth formation. The effectiveness of this procedure in areas in which fluoride occurs naturally has been known since the studies of Dean *et al.* (72). The protection thus afforded has been shown by Russell & Elvove (73) to last at least until 40 yrs. of age. Even an intermittent content of fluoride in the drinking water is effective [Bruce & Gunter (74)].

Evidence as to the effectiveness of artificial addition of 1 p.p.m. fluoride to drinking water continues to mount. The most recent reports of Arnold, Dean & Knutson (75) for Grand Rapids after 7 years of fluoridation show 66.6 per cent reduction in caries for the 6-year-old group and 18.1 per cent reduction in the 16-year-old group. Ast & Chase (76) report that after 6 years of the Newburgh-Kingston study there is a 59 per cent reduction in the 5-year-old group, and somewhat smaller percentages in the older groups.

Some doubt is often expressed as to possible harmful effects of ingestion over a prolonged period of even 1 p.p.m. fluoride. The Newburgh-Kingston studies show that there has been no difference in health or mortality rates since the study began. The extensive critical survey on the toxicity of fluorides by Heyroth (77) further demonstrates the safety of fluoridation of drinking water. There seems little danger even in those areas in which industrial processes deposit fluorides on the vegetation and poison cattle who eat this vegetation. The study of such an area by Savara, Noyes & Suher (78) showed that children living in such an area gave no evidence of any effect of fluoride.

Much attention has recently been devoted to the use of dentifrices which contain dibasic ammonium phosphate and urea. Preliminary studies by Kesel *et al.* (79) indicated that such dentifrices would reduce caries, and that the ammonium ion had a specific inhibiting action on the growth of lactobacillus. The use of such dentifrices required that the teeth be brushed with them immediately after eating, so that the ammonium ion could remain around the teeth and exert its effect. Fosdick (80) showed that this method of tooth brushing alone could reduce caries, and an extensive study by Kerr & Kesel (81) confirmed that such a tooth brushing technique reduced caries about 10 per cent. They found that the use of an ammoniated dentifrice gave about 10 per cent more caries reduction. Even this much effect was not found by Davies & King (82). Chernausek & Mitchell (83, 84) found that feeding ammonium phosphate to hamsters decreased caries, but the later study of Mitchell, Helman & Chernausek (85) indicated that sodium phosphate was also effective, suggesting that the buffering power of these salts was important. Wright & Jenkins (86) have noted a positive correlation between the concentration of ammonia in the saliva and its power to produce acid from glucose. Thus the theoretical basis for the use of ammoniated dentifrices is uncertain, and in practice they appear to produce at best only slight caries reduction.

Antibiotic dentifrices have been extensively studied. Webman, Hill & Knieser (87) observed in 1949 that penicillin dentifrices reduced caries in rats. Zander, Lisanti & Shiere (88) confirmed this in hamsters and showed that aureomycin and tyrothricin had little or no effect. Stephan *et al.* (89, 90) showed that penicillin was the only one of the antibiotics effective against rat caries. Studies in humans have shown that penicillin dentifrices reduce the lactobacillus count in most cases [Hill & Knieser (91), White, Knieser & Hill (92), Ludwick, Fosdick & Schantz (93)]. Zander (94) found a considerable reduction in caries among school children using a penicillin dentifrice. Lind & Zander (95) and Fitzgerald, Zander & Jordan (96) noted that use of such a dentifrice did not induce an acquired resistance to penicillin in groups of streptococci or staphylococci. Hill, Sims & Newman (97) and Welch *et al.* (98) however observed increased resistance among a number of oral organisms after use of penicillin dentifrices. As in animals, penicillin is the only effective antibiotic against caries [Ludwick & Fosdick (93, 99)]. The use of

antibiotic dentifrices has never been widespread, and it is rather doubtful if the possible advantages of their use can offset their disadvantages.

A few suggested methods for caries prevention have received considerable publicity, but have not yet proved themselves. Such are the use of chlorophyll dentifrices, whose value appears to be doubtful [Costich & Hein (100), Kutscher & Chilton (101)] and the effectiveness of nitrofurans, suggested by Dreizen, Greene & Spies (102, 103). Hufstader *et al.* (104) have not confirmed the value of these substances. The method of impregnating teeth with zinc chloride and potassium ferrocyanide has been shown by Dannenberg & Bibby (105) and by Ast, Bushel & Chase (106) to be ineffective.

Although fluorides remain at the present time the only tested agent whose effectiveness for caries reduction has been firmly established, studies are proceeding actively, and it is very probable that a combination of methods will eventually be developed which will go far towards eliminating dental caries as a public health problem.

LITERATURE CITED

1. Leicester, H. M., *Biochemistry of the Teeth* (Mosby Co., St. Louis, Mo., 306 pp., 1949)
2. Leicester, H. M., *Ann. Rev. Biochem.*, **22**, 341–50 (1953)
3. Bruce, K. W., and Stafne, E. W., *J. Am. Dental Assoc.*, **41**, 684–89 (1950)
4. Medak, H., Schour, I., and Klauber, W. A., Jr., *J. Dental Research*, **29**, 839–42 (1950)
5. Burstone, M. S., *J. Dental Research*, **29**, 220–31 (1950)
6. English, J. A., and Tullis, J. L., *J. Dental Research*, **30**, 33–52 (1951)
7. Dale, P. P., *J. Dental Research*, **32**, 117–25 (1953)
8. Medak, H., Weinreb, M., Sicher, H., Weinmann, J. P., and Schour, I., *J. Dental Research*, **31**, 559–74 (1952)
9. Burstone, M. S., *Arch. Pathol.*, **50**, 419–26 (1950)
10. Burstone, M. S., *Am. J. Pathol.*, **27**, 21–31 (1951)
11. Kalnins, V., *J. Dental Research*, **32**, 177–88 (1953)
12. Bagnall, J. S., *Bibliography on Caries Research* (National Research Council of Canada, Ottawa, Can., 557 pp., 1950)
13. Toverud, G., Cox, G. J., Finn, S. B., Bodecker, C. F., and Shaw, J. H., *A Survey of the Literature of Dental Caries* (National Academy of Sciences—National Research Council, Washington, D. C., 567 pp., 1952)
14. Shaw, J. H., *Intern. Dental. J.*, **1**, 48–74 (1950)
15. Frisbie, H. E., *Intern. Dental J.*, **1**, 13–31 (1950)
16. Boyd, J. D., Cheyne, V. D., and Wessells, K. E., *Proc. Soc. Exptl. Biol. Med.*, **71**, 535–37 (1949)
17. Boyd, J. D., Wessels, K. E., and Cheyne, V. D., *J. Dental Research*, **28**, 641–42 (1949)
18. Glass, R. L., *Oral. Surg., Oral. Med., Oral Pathol.*, **5**, 210–13 (1952)
19. Davies, E. E., *J. Am. Dental. Assoc.*, **40**, 37–45 (1950)
20. Parsons, E. I., McCollum, E. V., and Frobisher, M., *Am. J. Hyg.*, **44**, 249–56 (1946)

21. Shiere, F. R., Georgi, C. E., and Ireland, R. L., *J. Dental Research*, **30**, 116–25 (1951)
22. Fitzgerald, R. J., *J. Dental Research*, **31**, 189–94 (1952)
23. Harrison, R. W., *J. Am. Dental Assoc.*, **37**, 391–403 (1948)
24. Lammers, T., *Deutsche zahnärztl. Z.*, **8**, Part 2, 55–60 (1953)
25. Hurst, V., Nuckolls, J., and Frisbie, H. E., *J. Dental Research*, **28**, 668–69 (1949)
26. Onisi, M., and Nuckolls, J., *J. Dental Research*, **30**, 517–18 (1951)
27. Ennever, J., Robinson, H. B. G., and Kitchin, P. C., *J. Dental Research*, **30**, 88–96 (1951)
28. Strålfors, A., *J. Dental Research*, **27**, 576–86 (1948)
29. Ericsson, Y., and Hellström, I., *Acta Odontol. Scand.*, **10**, 118–33 (1953)
30. Wakeman, E. J., Smith, J. K., Zepplin, M., Sarles, W. B., and Phillips, P. H., *J. Dental Research*, **27**, 489–92 (1948)
31. Hartles, R. L., and McLean, N. D., *Brit. Dental J.*, **93**, 147–50 (1952)
32. Pincus, P., *Exptl. Med. and Surg.*, **8**, 308–10 (1950)
33. Evans, D. G., and Prophet, A. S., *Lancet*, **I**, 290–93 (1950)
34. Evans, D. G., and Prophet, A. S., *J. Gen. Microbiol.*, **4**, 360–64 (1950)
35. Prophet, A. S., and Atkinson, H. F., *Brit. Dental J.*, **94**, 278–81 (1953)
36. Engel, M. B., *J. Am. Dental. Assoc.*, **40**, 284–94 (1950)
37. Coolidge, T., *J. Dental Research*, **30**, 480 (1951)
38. Burnett, G. W., and Scherp, H. W., *J. Dental Research*, **32**, 46–56 (1953)
39. Koser, S. A., and Fisher, B. J., *J. Dental Research*, **29**, 760–73 (1950)
40. Koser, S. A., Fisher, B. J., and Kauffman, S. L., *J. Dental Research*, **30**, 532–41 (1951)
41. Dreizen, S., and Spies, T. D., *J. Dental Research*, **32**, 65–73 (1953)
42. Dreizen, S., Reed, A. I., and Spies, T. D., *Intern. Z. Vitaminforsch.*, **22**, 396–401 (1951)
43. Dreizen, S., Reed, A. I., and Spies, T. D., *J. Dental Research*, **29**, 774–78 (1950)
44. Stephan, R. M., *J. Am. Dental Assoc.*, **37**, 530–36 (1948)
45. Shafer, W. G., *Science*, **110**, 143–44 (1949)
46. Orland, F. J., *Science*, **111**, 476 (1950)
47. Cartier, A., Cartier, P., and Picard, J., *Rev. Stomat.*, **53**, 107–22 (1952)
48. Wynn, W., Haldi, J., Shaw, J. H., and Sognnaes, R. F., *J. Nutrition*, **50**, 267–74 (1953)
49. Granados, H., Glavind, J., and Dam, H., *J. Dental Research*, **28**, 77–82 (1949)
50. Zepplin, M., Smith, J. K., Parsons, H. T., Phillips, J. H., and Elvehjem, C. A., *J. Nutrition*, **40**, 203–11 (1950)
51. Haldi, J., Wynn, W., Shaw, J. H., and Sognnaes, R. F., *J. Nutrition*, **49**, 295–306 (1953)
52. Neuwirth, I., and Summerson, W. H., *J. Dental Research*, **30**, 100–11 (1951)
53. Calandra, J. C., and Adams, E. C., *J. Dental Research*, **30**, 229–34 (1951)
54. Anderson, E. P., Smith, J. K., Elvehjem, C. A., and Phillips, P. H., *Proc. Soc. Exptl. Biol. Med.*, **66**, 67–69 (1947)
55. Anderson, E. P., Smith, J. K., Elvehjem, C. A., and Phillips, P. H., *J. Nutrition*, **35**, 371–77 (1948)
56. Constant, M. A., Phillips, P. H., and Elvehjem, C. A., *J. Nutrition*, **46**, 271–80 (1952)
57. McClure, F. J., and Folk, J. E., *Proc. Soc. Exptl. Biol. Med.*, **83**, 21–26 (1953)

58. Nizel, A. E., and Harris, R. S., *J. Dental Research*, **30**, 485 (1951)
59. Nizel, A. E., and Harris, R. S., *New Engl. J. Med.*, **244**, 361–62 (1951)
60. Sognnaes, R. F., *J. Nutrition*, **36**, 1–13 (1948)
61. Shaw, J. H., *Proc. Soc. Exptl. Biol. Med.*, **70**, 479–83 (1949)
62. Sognnaes, R. F., *J. Am. Dental Assoc.*, **37**, 677–92 (1948)
63. Sognnaes, R. F., *Brit. Dental J.*, **87**, 291–4 (1949)
64. Bransby, E. R., and Knowles, E. M., *Brit. Dental J.*, **87**, 236–43 (1949)
65. Hartles, R. L., *Biochem. J. (London)*, **48**, 245–49 (1951)
66. Herrmann, M., and Cremer, H. D., *Deutsche zahnärztl. Z.*, **8**, Part 2, 61–68 (1953)
67. Knutson, J. W., and Scholz, G. C., *Public Health Repts.*, **64**, 1403–10 (1949)
68. Klinkenberg, E., and Bibby, B. G., *J. Dental Research*, **29**, 4–7 (1950)
69. Rickles, N. H., *J. Dental Research*, **30**, 519–20 (1951)
70. Marshall-Day, C. D., *J. Dental Research*, **30**, 514 (1951)
71. Kutler, B., and Ireland, R. L., *J. Dental Research*, **31**, 493–94 (1952)
72. Dean, H. T., Jay, P., Arnold, F. A., Jr., and Elvove, E., *Public Health Repts.*, **56**, 761–92 (1941)
73. Russell, A. L., and Elvove, D., *Public Health Repts.*, **66**, 1389–1401 (1951)
74. Bruce, H. W., and Gunter, B. F., *J. Dental Research*, **32**, 35–45 (1953)
75. Arnold, F. A., Jr., Dean, H. T., and Knutson, J. W., *Public Health Repts.*, **68**, 141–48 (1953)
76. Ast, D. B., and Chase, H. C., *Oral Surg., Oral Med., Oral Pathol.*, **6**, 114–23 (1953)
77. Heyroth, F. F., *Am. J. Public Health*, **42**, 1568–75 (1952)
78. Savara, B. S., Noyes, H. J., and Suher, T., *J. Dental Research*, **31**, 493 (1952)
79. Kesel, R. G., Kirch, E. R., O'Donnell, J. F., and Wach, E. C., *Oral Surg., Oral Med., Oral Pathol.*, **2**, 459–73 (1949)
80. Fosdick, L. S., *J. Am. Dental Assoc.*, **40**, 133–43 (1950)
81. Kerr, D. W., and Kesel, R. G., *J. Am. Dental Assoc.*, **42**, 180–88 (1951)
82. Davies, G. N., and King, R. M., *J. Dental Research*, **30**, 645–55 (1951)
83. Chernausek, D. S., and Mitchell, D. F., *Science*, **112**, 273–74 (1950)
84. Chernausek, D. S., and Mitchell, D. F., *J. Dental Research*, **30**, 393–98 (1951)
85. Mitchell, D. F., Helman, E. Z., and Chernausek, D. S., *Science*, **116**, 537–38 (1952)
86. Wright, D. E., and Jenkins, G. N., *J. Dental Research*, **32**, 232–38 (1953)
87. Webman, H., Hill, T. J., and Knieser, A. H., *J. Dental Research*, **28**, 258–62 (1949)
88. Zander, H. A., Lisanti, V. F., and Shiere, F. R., *J. Dental Research*, **30**, 139–44 (1951)
89. Stephan, R. M., Harris, M. R., and Fitzgerald, R. J., *J. Dental Research*, **31**, 475 (1952)
90. Stephan, R. M., Fitzgerald, R. J., McClure, F. J., Harris, M. R., and Jordan, H., *J. Dental Research*, **31**, 421–27 (1952)
91. Hill, T. J., and Knieser, A. H., *J. Dental Research*, **27**, 744 (1948)
92. White, B. J., Knieser, A. H., and Hill, T. J., *J. Dental Research*, **28**, 267–71 (1949)
93. Ludwick, W. E., Fosdick, L. S., and Schantz, C. W., *J. Am. Dental Assoc.*, **43**, 285–89 (1951)
94. Zander, H. A., *J. Am. Dental Assoc.*, **40**, 569–74 (1950)

95. Lind, H. E., and Zander, H. A., *J. Dental Research*, **30**, 112–15 (1951)

96. Fitzgerald, R. J., Zander, H. A., and Jordan, H. V., *J. Am. Dental Assoc.*, **41**, 62–65 (1950)

97. Hill, T. J., Sims, J., and Newman, M., *J. Dental Research*, **31**, 461 (1952)

98. Welch, H., Randall, W. A., Putnam, L. E., and Hendricks, F. D., *Antibiotics & Chemotherapy*, **2**, 249–54 (1952)

99. Ludwick, W. E., and Fosdick, L. S., *J. Dental Research*, **30**, 470 (1951)

100. Costich, E. R., and Hein, J. W., *J. Dental Research*, **31**, 474–75 (1952)

101. Kutscher, A. H., and Chilton, N. W., *J. Am. Dental Assoc.*, **46**, 420–22 (1953)

102. Dreizen, S., Greene, H. I., and Spies, T. D., *J. Dental Research*, **28**, 288–97 (1949)

103. Dreizen, S., Greene, H. I., and Spies, T. D., *Proc. Soc. Exptl. Biol. Med.*, **70**, 558–61 (1949)

104. Hufstader, R. D., Anderson, V. J., Phatek, N., and Snyder, M. L., *J. Dental Research*, **29**, 794–97 (1950)

105. Dannenberg, J. L., and Bibby, B. G., *J. Dental Research*, **29**, 177–78 (1950)

106. Ast, D. B., Bushel, A., and Chase, H. C., *J. Am. Dental Assoc.*, **41**, 437–42 (1950)

ANNOTATED LIST OF REVIEWS IN MEDICINE

By Eaton M. MacKay[1]

For the most part the reviews listed apply to the field of clinical medicine. Some are more pertinent to the preclinical sciences and are included for the benefit of clinical physiologists and clinical investigators.

Reviews differ greatly in the extent and nature of their coverage. Some review the literature in a given field, and others review a subject or an extensive contribution to a subject. Those comprising the *Annual Review of Physiology* and the other sister series of this volume, which are devoted to the preclinical sciences, as well as the regular clinical series appearing in several of the *Archives* journals published by the American Medical Association, cover the literature of the stated field or subject for the preceding one or two years. The reviews in *Physiological Reviews, Medicine,* and several of the *Recent Advance's* series tend to be comprehensive reviews of a limited subject, the literature covered frequently extending over many years, even to an historical background. Other reviews are bibliographical, sometimes with a systematic but simple listing of references and others with critical abstracts. With few exceptions the reviews chosen for this list are in English, partly for obvious reasons, and in part because satisfactory reviews in foreign languages have been scarce since the late 1930's. Numerous reviews come from the "original articles" literature where a good summary of previously reported cases or the literature of the subject is included with a report of new data. A few of the reviews listed cover only the data of the author and are included because they are timely and have an extensive basis.

Reviews selected from the *British Medical Journal* or the *Annals of the Royal College of Surgeons* generally represent a formal lecture or a condensation thereof. They tend to cover a subject and not the literature, but are concise, usually authoritative, and as a rule unusually well written. For the first time articles from the *Journal of the American Medical Association* are listed because they review an important topic. They are rarely reviews of the literature but when the latter is well covered, it avails the reader little for this journal has a peculiar practice of listing bibliographic references only in the author's reprints and not in the *Journal* article!

Comments on the reviews indicate the impression of the compiler when he happened to peruse them. The absence of any comment should not be looked on in a prejudicial manner. The lack may have been a result of difficult accessibility, press of other matters, an uncertainty as to its value, or a decision that suitable comment would have to be too long. The reviews from the *Annual Review* series are generally left without comment for their high standard of quality is well-known. The selection and relative emphasis given the reviews listed is attributable solely to the compiler, and we make no apology for inclusions or exclusions nor the idiosyncrasies which may have been responsible for them.

[1] Address: Beverly Hills Clinic, 133 South Lasky Drive, Beverly Hills, California.

INFECTIOUS DISEASES

1. "Infectious Diseases," Reimann, H. A., *Arch. Internal Med.*, **91**, 353–88 (1953), 247 references. A careful survey of the recent literature.

2. "A Bibliography of Internal Medicine: Scarlet Fever," Bloomfield, A. L., *Stanford, Med. Bull.*, **10**, 114–29 (1952), 92 references. The "references" are interesting and authoritative abstracts with critical comments which trace the development of our knowledge of scarlet fever, a most important review of the disease.

3. "Present State of Knowledge Concerning Pathogenesis and Treatment of Rheumatic Fever," McCarty, M., *Bull. N. Y. Acad. Med.*, **28**, 307–20 (1952), 17 references. An excellent short summary.

4. "A Symposium on Hemorrhagic Fever," *Ann. Internal Med.*, **38**, 53–112 (1953), seven articles by fifteen authors, 15 references. A discussion of a disease entity encountered in Korea which is new to Americans but known to the Japanese in Manchuria.

5. "Clinical Manifestations of Epidemic Hemorrhagic Fever," Powell, G. M. *J. Am. Med. Assoc.*, **151**, 1261–64 (1953), no references.

6. "Aseptic Meningitis, A Disease of Diverse Etiology," Adair, C. V., Gauld, R. L., and Smadel, J. E., *Ann. Internal Med.*, **39**, 675–704 (1953), 67 References. A review of an 11 year series covering clinical and etiologic studies on 854 cases.

7. "Tuberculosis: Incidence among American Medical Students, Prevention and Control and the Use of BCG," Abruzzi, W. A., Jr., and Hummel, R. J., *New Engl. J. Med.*, **248**, 723–29 (1953), 104 references. An important survey.

8. "Syphilis," Beerman, H., Schamberg, I. L., Nicolas, L., and Katzenstein, L., *Arch. Internal Med.*, **91**, 493–540, 633–74 (1953), 323 references. A review of the recent literature which gives evidence of a rapidly decreasing interest and incidence of syphilis in the United States in comparison with much of the world.

9. "Varicella-Encephalitis," Appelbaum, E., Rachelson, M. H., and Dolgopol, V. B., *Am. J. Med.*, **15**, 223–30 (1953), 25 references. An analysis of 59 cases.

10. "A Bibliograpy of Internal Medicine: Poliomyelitis," Bloomfield, A. L., *Stanford Med. Bull.*, **11**, 79–90 (1953), 22 references. A scholarly review through critical summaries of the significant literature of the fundamental and historical development of our knowledge about poliomyelitis from 1800 to its experimental transmission in 1909.

11. "Differential Diagnosis of Poliomyelitis," Grulee, C. G., Jr., *J. Am. Med. Assoc.* **152**, 1587–92, (1953), 9 references.

12. "The Epidemiology and Pathogenesis of Poliomyelitis", Horstmann, D. M., *Bull. N. Y. Acad. Med.*, **29**, 910–29 (1953), 46 references. An explanation of the pathogenesis of this disease is offered as an hypothesis to be proved or disproved.

13. "Passive Immunization Against Poliomyelitis with Especial Consideration of the Effectiveness of Gamma Globulin," Hammon, W. M., *Bull. N. Y. Acad. Med.*, **29**, 930–42 (1953), 4 references.

14. "Active Immunization Against Poliomyelitis," Cox, H. R., *Bull. N. Y. Acad. Med.*, **29**, 943–60 (1953), 92 references.

15. "Present Status and Future Possibilities of a Vaccine for the Control of Poliomyelitis," Sabin, A. B., *Am. J. Diseases Children*, **86**, 301–10 (1953), 20 references.

16. "Recent Progress in Poliomyelitis Research," Ward, R., *J. Pediat.*, **43**, 98–107 (1953), 59 references. Reviews recent developments.

17. "A Bibliography of Internal Medicine: Influenza," Bloomfield, A. L., *Stanford Med. Bull.*, **10**, 293–303 (1952), 30 references. Another welcome addition to the diseases being covered in Professor Bloomfield's project.

18. "Influenza: The Newe Acquayntance," Francis, T., Jr. *Ann. Internal Med.*, **39**, 203–21 (1953), 38 references. A review of the "influenza of 1918" in relation to our knowledge of influenza and influenza viruses.

19. "Viral Hepatitis," Gellis, S. S., and Hsia, D. Y-Y., *New Engl. J. Med.*, **249**, 400–9 (1953), 129 references. A very good review of its current status.

20. "Malaria During the Last Decade", Young, M. D., *Am. J. Trop. Med., Hyg.*, **2**, 347–59 (1953), 78 references. A review concerned with human malaria and the more significant developments.

21. "Antibiotics in Acute Bacillary Dysentery," Garfinkle, B. T., Martin, G. M., Watt, J., Payne, F. J., Mason, R. P., and Hardy, A. V., *J. Am. Med. Assoc.* **151**, 1157–59 (1953), 7 references. A review of 1408 cases.

22. "Comparative Efficacy of Amebacides and Antibiotics in Acute Amoebic Dysentery," Martin, G, A., Garfinkel, B. T., Brooke, M. M., Weinstein, P. P., and Frye, W. W., *J. Am. Med. Assoc.* **151**, 1055–59 (1953), 6 references. A series of 538 cases.

23. "Amebiasis," Porter, R. J., *Ann. Rev. Microbiol*, **7**, 273–94 (1953), 160 references.

24. "Mycology," Jillson, O. F., *New England J. Med.*, **249**, 523–30, 561–66 (1953), 197 references. Clinical aspects are well covered.

25. "Medical Mycology," Nickerson, W. J., *Ann. Rev. Microbiol.*, **7**, 245–72 (1953), 245 references.

26. "Adrenocortical Hormones in Infection and Immunity," Kass, E. H., and Finland, M., *Ann. Rev. Microbiol.*, **7**, 361–88 (1953), 313 references.

27. "Helminths: Metabolism, Nutrition and Chemotherapy," Bueding, E., and Most, H., *Ann. Rev. Microbiol*, **7**, 295–326 (1953), 187 references.

28. "Antibotic-Resistant Staphylococci and Related Infections," Pressick, F. H., *Am. J. Med. Sci.*, **225**, 299–319 (1953), 108 references. The opinions and conclusions representative of the literature of the past five years are correlated and discussed.

29. "Acid Fast Bacteria," Block, H., *Ann. Rev. Microbiol.*, **7**, 19–46 (1953), 218 references.

30. "Nutrition of Microorganisms," Cheldelin, V. H., and King, T. E., *Ann Rev. Microbiol.*, **7,** 113–42 (1953), 239 references.

31. "Metabolism of Microorganisms," Stadtman, E. R., and Stadtman, T. C., *Ann Rev. Microbiol.*, **7,** 143–78 (1953), 234 references.

32. "Virus and Rickettsial Classification and Nomenclature," 31 papers by Burnet, M. *et al.*, *Ann. N. Y. Acad. Sci.*, **56,** 381–622 (1953), 424 references. A detailed all inclusive symposium.

33. "Developmental Stages of Viruses," Schlesinger, R. W., *Ann. Rev. Microbiol.*, **7,** 83–112 (1953), 197 references.

34. "Biochemical Aspects of Viral Growth," Pearson, H. E., *Ann. Rev. Microbiol.*, **7,** 179–96 (1953), 139 references.

35. "Viral and Rickettsial Toxins," Cox, H. R., *Ann Rev. Microbiol.*, **7,** 197–218 (1953), 78 references.

36. "Food Poisoning," Dack, G. M., *Ann. Rev. Microbiol.*, **7,** 327–38 (1953), 68 references.

PUBLIC HEALTH

1. "Contributions of the Social Sciences to the Solution of Health Problems," Leavell, H. R., *New Engl. J. Med.*, **247,** 885–97 (1952), 135 references. A provocative review.

2. "Medicine and Social Policy," Crew, F. A. E., *Brit. Med. J.*, **32,** 1123–28 (1953), no references. An interesting discussion of a lively topic.

3. "World Population Problems and Birth Control," a symposium of 15 papers by Hartman, C. G. *et al.*, *Ann. N. Y. Acad. Sci.*, **54,** 729–95 (1952), 115 references.

4. "The Effect of Aging of Population on General Health Problems," Monroe, R. T., *New Engl. J. Med.*, **249,** 277–85, 322–28 (1953), 24 references. A review which points up numerous problems which need answers.

5. "Health in Colleges," Farnsworth, D. L., *New Engl. J. Med.*, **248,** 543–52 (1953), 29 references. A conservative consideration of the problem.

6. "Nutrition Research and the Public Health Program," Pett, L. B., *Borden's Rev. Nutrition Research*, **14,** 45–59 (1953), 60 references. An attempt to define public health nutrition.

7. "Epidemiological Aspects of Gamma Globulin Prophylaxis in Poliomyelitis," Bell, J. A., *Am. J. Diseases Children*, **80,** 311–18 (1953), 6 references. The author's evaluation of published and unpublished data pertinent to this use of gamma globulin.

8. "Vectors and Reservoirs of Virus Disease," Meyer, K. F., *Am. J. Trop. Med. Hyg.*, **2,** 757–70 (1953), 31 references. A superior brief general survey.

9. "The Ecology of Mosquito Borne Viruses," Eklund, C. M., *Ann. Rev. Microbiol.*, **7,** 339–60 (1953), 114 references.

10. "Synergism and Antagonism in Mass Disease of Man," Taylor, A. E., and Gordon, J. E., *Am. J. Med. Sci.*, **225,** 320–44 (1953), 204 references. A provocative review of the relation to and influence on one disease by another.

11. "Microbiology of Water and Sewage," Heukelekian, H., *Ann. Rev. Microbiol.*, **7**, 461–72 (1953), 91 references.

DISEASES OF THE GASTROINTESTINAL TRACT

1. "The Digestive System," Code, C. F., *Ann. Rev. Physiol.*, **15**, 107–38 (1953), 222 references.

2. "Physiology and Pharmacology of Vomiting," Borison, H. L., and Wang, S. C., *Pharmacol. Revs.*, **5**, 193–230 (1953), 194 references. A thorough review of our present knowledge of the subject.

3. "Liver," Mann, F. C., and Mann, F. D., *Ann. Rev. Physiol.*, **15**, 473–92 (1953), 155 references.

4. "Acute Postoperative Dilation of the Stomach," Starr, K. W., *Ann. Roy. Coll. Surg. England*, **12**, 71–87 (1953), 45 references. An excellent summary of the water and electrolyte circulation associated with digestion.

5. "Polyps and Adenomas of the Stomach," Hay, L. J., *Surgery*, **33**, 446–67 (1953), 24 references. A personal study.

6. "Hormones and Peptic Ulcer," Kirsner, J. B., *Bull. N. Y. Acad. Med.*, **29**, 477–504 (1953), 151 references. A critical review of the available data in the human.

7. "On the Ischemic Basis of 'Peptic' Ulcer," Palmer, E. D., and Buchanan, D. P., *Ann Internal Med.*, **38**, 1187–1205, (1953), 135 references. An historical definition of its present status.

8. "Recent Advances in the Medical Management of Peptic Ulcer," Flood, C. A., *Bull. N. Y. Acad. Med.*, **28**, 773–84 (1953), 30 references. An evaluation of new methods of treatment.

9. "Treatment of Peptic Ulcer," Zetzel, L., *New Engl. J. Med.*, **248**, 976–82, 1015–21, (1953), 161 references. Recent progress in the medical treatment and the merits of surgical treatment are fairly reviewed.

10. "Recent Developments in the Surgery of Peptic Ulcer," Colp, R., *Bull. N. Y. Acad. Med.*, **28**, 785–95 (1953), 11 references. A fair consideration of surgical treatment.

11. "Vagotomy as a Prophylactic and Curative Procedure in Peptic Ulcer," Walters, W., and Chance, D. P., *J. Am. Med. Assoc.*, **153**, 993–97 (1953), 15 references. A critical summary.

12. "Carcinoma of the Stomach," Ochsner, A., and Blalock, J., *J. Am. Med. Assoc.*, **151**, 1377–84 (1953). A comprehensive statistical review emphasizing the necessity for reevaluation of therapeutic philosophy.

13. "Carcinoma of Stomach," Boyce, F. F., *J. Am. Med. Assoc.*, **151**, 15–20 (1953), 12 references. A comparison of three series of cases coming to surgery.

14. "Colonic Replacement and Restoration of the Human Stomach," Moroney, J., *Ann. Roy. Coll. Surg. England*, **12**, 328–48 (1953), 3 references. A review of experience in replacing the stomach with a loop of colon after gastric resection.

15. "Nonparasitic Benign Cystic Tumors of the Spleen," Fowler, R. H.,

Intern. Abstr. Surg., **96**, 209–27 (1953), 107 references. A complete review of the old and recent literature.

16. "Hydatid Cysts of the Spleen," Fowler, R. H., *Intern. Abstr. Surg.*, **96**, 105-16 (1953), 233 references. A complete review of all the literature.

17. "Annular Pancreas," Moore, T. C., *Surgery*, **33**, 138–48 (1953), 64 references. A review of the pertinent literature.

18. "The Differential Diagnosis of Pancreatic & Renal Disease, with Particular Emphasis on Differentiating Pancreatic Cysts from Renal Cysts," Abeshouse, B. S., *Intern. Abstr. Surg.*, **96**, 1–28 (1953), 105 references. A review of the literature for many years past as well as a very extensive experience.

19. "Colonic & Anorectal Function and Disease," Turell, R., Krakauer, J. S., and de L. Maynard, A., *Intern. Abstr. Surg.*, **96**, 313–39, 417–49 (1953), 402 references. A collective review of the past three years' literature.

20. "Problems in Ulcerative Colitis," Machella, T. E., *Am. J. Med.*, **13**, 760–76 (1952), 216 references. Many problems presented by this ailment are completely reviewed.

21. "The Development of Surgery for Ulcerative Colitis," Brooke, B. N., *Ann. Roy. Coll. Surg. England*, **12**, 246–58 (1953), 14 references. A survey of English experience.

DISEASES OF THE CARDIOVASCULAR SYSTEM

1. "Needless Restrictions Imposed on Cardiac Patients," Levy, R. L., *Circulation*, **5**, 454-61 (1952), 35 references. A review of the basis for more lenient requirements for these patients. Designed for all practitioners.

2. "The Patient with Cardiovascular Disease and Rehabilitation: The Third Phase of Medical Care," Benton, J. G., and Rusk, H. A., *Circulation*, **8**, 417–26 (1953), 30 references. A positive review of a very practical subject.

3. "The Management of Congestive Heart Failure," Blumgart, H. L., *Circulation*, **7**, 127–38 (1953), 17 references. Summary of current procedures presented in a manner of general interest.

4. "Diagnosis & Management of Common Malformations of the Heart," Taussig, H. B., *Circulation*, **6**, 930–40 (1952), 23 references. A working review.

5. "Heart," Fishman, A. P., and Cournand, A., *Ann Rev. Physiol.*, **15**, 247–82 (1953), 401 references.

6. "Aspects of Cardiac Hypertrophy," Grant, R. P., *Am. Heart J.*, **46**, 154–58 (1953), 40 references. A very brief summary of the current status of the subject.

7. "Treatment of Cardiac Arrhythmias," Scherf, D., *Circulation*, **8**, 756–68 (1953), 40 references. A review emphasizing the controversial points in the therapy of refractory arrhythmias.

8. "The Nature of Auricular Fibrillation and Flutter: A Symposium," Blumgart, H. L., Hecht, H., Katz, L. N., Pick, A., Prinzmetal, M. and Rosenblueth, A., *Circulation*, **7**, 591–600 (1953) 43 references. The mechanisms are reviewed by three different sets of authors.

9. "The Thyroid and the Circulation," Andrus, E. C., *Circulation*, **7**, 437-44 (1953), 49 references. A brief summary of the subject of interest to all internists.

10. "Radioiodine in Treatment of Advanced Heart Disease," Jaffe, H. L., Rosenfeld, M. H., Pobirs, F. W., and Stuppy, L. J., *J. Am. Med. Assoc.*, **151**, 716–20 (1953), 11 references. A summary of the results in 100 patients.

11. "Hypertension," Wilkins, R. W., and Stucki. P., *Arch Internal Med.*, **91**, 118–37 (1953), 158 references. An excellent synposis of the literature on hypertension from July 1, 1950 to January 1, 1952.

12. "The Medical Management of Arterial Hypertension," Meilman, E., *New Engl. J. Med.*, **248**, 894–902, 936–43 (1953), 222 references. An evaluation of various hypotensive agents or regimes.

13. "Course and Prognosis of Essential Hypertension," Palmer, R. S., and Muench, H., *J. Am. Med. Assoc.*, **153**, 1–4 (1953), 6 references. An analysis of 450 patients 10 years after the discovery of the ailment.

14. "Endocrine Factors in Hypertension," Perera, G. A., *Bull. N. Y. Acad. Med.*, **28**, 43–51 (1952), 12 references. A short summary of new developments.

15. "Splanchniectomy for Essential Hypertension," Smithwick, R. H., and Thompson, J. E., *J. Am. Med. Assoc.*, **153**, 1501–6 (1953), 4 references. A summary of the results in 1266 cases.

16. "Hypertension and Relation Between Kidney Weight and Body Weight," Braun-Menendez, E., *Stanford Med. Bull.*, **10**, 65–75 (1952), 65 references. An intriguing hypothesis is presented.

17. "Experimental Hypertension," Green, D. M., *Ann. Internal Med.*, **39**, 333–44 (1953), 128 references. An excellent review of the relation of various types of experimental hypertension in animals to essential hypertension in man.

18. "The Relation of Cardiac Catheterization to Cardiovascular Surgery," Lukas, D. S., *Bull. N. Y. Acad. Med.*, **29**, 668–76 (1953), 15 references. An enthusiastic appraisal.

19. "The Surgical Therapy of Acquired Heart Disease," Lam, C. R., *Quart Rev. Surg.*, **9**, 1–9 (1952), 68 references. A brief discussion of the subject.

20. "The Surgery of Acquired Valvular Heart Disease," Kramer, M., *Am. J. Med. Sci.*, **225**, 565–78 (1953), 84 references. A review of the rapid rise in this therapy during the past five years.

21. "Mitral Commissurotomy," Glenn, F., and Stewart, J., *Bull. N. Y. Acad. Med.*, **29**, 677–83 (1953), 9 references. A careful evaluation of the present place of the procedure.

22. "The Treatment of Chronic Cor Pulmonale," Harvey, R. M., Ferrer, M. I., and Cournand, A., *Circulation*, **7**, 932–40 (1953), 19 references. Modern concepts of therapy are emphasized.

23. "Mortality, Morbidity and Treatment of Myocardial Infarction," Wooten, R. L., and Kyser, F. A., *Ann. Internal Med.*, **38**, 247–53 (1953), 14 references. A review of the authors' series of 455 cases.

24. "Treatment of Angina Pectoris," Uricchio, J. F., and Calenda, D. G., *New Engl. J. Med.*, **249,** 689–98 (1953), 172 references. A review of the literature emphasizing the advances of the past several years.

25. "Ballistocardiography," Gubner, R. S., Rodstein, M., and Ungerleider, H. E., *Circulation*, **7,** 268–86 (1953), 71 references. An appraisal of technic, physiologic principles, and clinical value.

26. "A Review of Ballistocardiography," Scarborough, W. R., Davis, F. W., Jr., Baker, B. M., Jr., Mason, R. E., and Singewald, M. L., *Am. Heart J.*, **44,** 910–46 (1952), 170 references. A not too technical review which points out possible future possibilities of this procedure.

27. "Vectorcardiography," Burch, G. E., Abildskov, J. A., and Cronvich, J. A., *Circulation*, **8,** 605–13 (1953), 40 references. For the electrocardiographic specialist in physiology and perhaps someday cardiology.

28. "Spatial Vectorcardiography," Wolff, L., Richman, J. L., and Soffe, A. M., *New Engl. J. Med.*, **248,** 810–19, 851–57 (1953), 76 references. A detailed review of a highly specialized technical subject.

29. "Electrokymography: The Ventricular Electrokymogram," Dack, S., and Paley, D. H., *Am. J. Med.*, **12,** 331–48 (1952), 45 references. A new experimental method of studying cardiac pulsations.

30. "Spatial Vectorcardiography," Grishman, A., Scherlis, L., and Lasser, R. P., *Am. J. Med.*, **14,** 184–200 (1953), 42 references. For the investigator of the electrocardiogram.

31. "Diagnosis and Prevention of Bacterial Endocarditis," Bloomfield, A. L., *Circulation*, **8,** 290–96 (1953), 24 references. A lucid easy reading and useful review of the subject worth the time of any clinician.

32. "Present Day Treatment of Subacute Bacterial Endocarditis," Keefer, C. S., *J. Am. Med. Assoc.*, **152,** 1397–1400 (1953), 10 references.

33. "Atherosclerosis. A Symposium," Allen, E. V., Katz, L. N., Keys, A., and Gofman, J. W., *Circulation*, **5,** 98–134 (1952), 12 references. A review and discussion of current hypotheses largely for the clinical investigator.

34. "Lipid Metabolism and Atherosclerosis," Kellner, A., *Bull. N. Y. Acad. Med.*, **28,** 11–27 (1952), 72 references. New theories and evidence is critically assayed.

35. "Diet and Lipotrophic Agents in Atherosclerosis," Gofman, J. W., *Bull. N. Y. Acad. Med.*, **28,** 279–93 (1952), 12 references. A discussion by the original investigator of the present status of lipoproteins in relation to this ailment.

36. "Coarctation of the Aorta," Gross, R. E., *Circulation*, **7,** 757–68 (1953), 23 references. A useful summarization of the available information.

37. "Coarctation of the Aorta," O'Sullivan, W. D., and Steinberg, I., *Bull. N. Y. Acad. Med.*, **29,** 687–93 (1953), 11 references. An optimistic summary of the surgical treatment of this ailment.

38. "Aortic Arch Syndromes," Ross, R. S., and McKusick, V. A., *Arch. Internal Med.*, **92,** 701–40 (1953), 146 references. A review of 65 cases from the literature and 35 additional ones of diminished or absent pulses in arteries arising from the arch of the aorta.

39. "Aneurysm of the Splenic Artery," Owens, J. E., and Coffey, R. J., *Intern. Abstr. Surg.*, **97**, 313–35 (1953), 182 references. A review of 198 recorded cases in the literature of 182 years with a report of 6 new ones.

40. "Periarteritis Nodosa and Other Forms of Necrotizing Angitis," Zeek, P. M., *New Engl. J. Med.*, **248**, 764–72 (1953), 76 references. An important critical review of a currently confused subject.

41. "The Place of Sympathectomy in Peripheral Vascular Disease," Cohen, S. M., *Ann. Roy. Coll. Surg. England*, **12**, 96–116, (1953), 44 references. A critical evaluation of use and technique.

42. "The Definitive Surgery of Major Vessels," Gerbode, F., *Quart. Rev. Surg.*, **9**, 59–68 (1952), 106 references. A general expression of the present methods of treatment.

43. "Medical Management of Peripheral Arterial Occlusive Diseases," Wessler, S., *New Engl. J. Med.*, **249**, 233–45 (1953), 221 references. A critical summary of the present status of the subject.

44. "Highlights in the Treatment of Varicose Veins and Ulcers," Summers, J. E., *Am. J. Surg.*, **86**, 443–63 (1953), 160 references. An historical survey which covers current methods of therapy.

45. "Peripheral Circulation," Burton, A. C., *Ann. Rev. Physiol.*, **15**, 213–46 (1953), 221 references.

46. "Blood Volume Maintenance and Regulation," Ravdin, I. S., Walker, J. M., and Rhoads, J. E., *Ann. Rev. Physiol.*, **15**, 165–94 (1953), 198 references.

47. "Volume and Distribution of Blood and Their Significance in Regulating Circulation," Sjöstrand, T., *Physiol. Rev.*, **33**, 202–28 (1953), 124 references. A review which attempts to clarify the importance of variations in blood volume as a regulatory factor. For the clinical physiologist.

48. "Homeostatic Limits to Safe Parenteral Fluid Therapy," Talbot, N. B., Crawford, J. D., and Butler, A. M., *New Engl. J. Med.*, **248**, 1100–8 (1953), 54 references. A most useful albeit somewhat technical summary.

49. "Some Relations Between Skin Temperature and Blood Flow," Hertzman, A. B., *Am. J. Physical. Med.*, **32**, 233–51 (1953), 33 references. The subject is very well covered with citations of the readily available literature.

DISEASES OF THE URINARY SYSTEM

1. "Urology," Colby, F. H., *New Engl. J. Med.*, **248**, 628–89 (1953), 42 references. A brief review of recent developments.

2. "Gross Urinary Hemorrhage: A Symptom, Not a Disease," Lee, L. W., and Davis, E., Jr., *J. Am. Med. Assoc.*, **153**, 782–84 (1953). A statistical review of the data on 1000 patients.

3. "The Physiologic and Clinical Significance of Immaturity on Kidney Function in Young Infants," Barnett, H. L., and Vesterdal, J., *J. Pediat.*, **42**, 99–119 (1953), 58 references. A review for the renal physiologist.

4. "The Clinical Course of Acute Renal Failure," Swann, R. C., and Merrill, J. P., *Medicine*, **32**, 215–92 (1953), 156 references. A review of the literature and observations on a series of 85 patients.

5. "Management of Acute Glomerulonephritis," Derow, H. A., *New Engl. J. Med.*, **249**, 144–53 (1953), 106 references. A complete detailed summary.

6. "Edema of Acute Nephritis," Peters, J. P., *Am. J. Med.*, **14**, 448–58 (1953), 27 references. A concise critical review of the subject based on 300 patients over a 30 year period.

7. "Outlook for Patients with Glomerulonephritis," Keith, N. M., and Odel, H. M., *J. Am. Med. Assoc.*, **153**, 1240–45 (1953), 18 references. A brief analysis of present information about prognosis.

8. "Acute Nephrosis: The Kidney of Acute Renal Failure," Waugh, D., *Am. J. Med. Sci.*, **226**, 310–25 (1953), 177 references. A complete review of the literature outlining the principal concepts of the pathogenesis as well as the extent and character of the kidney lesions.

9. "Advances in Management of the Nephrotic State," Luetscher, J. A., Jr., Deming, Q, B., Johnson, B. B., and Piel, C. F., *J. Am. Med. Assoc.*, **153**, 1236–39 (1953), 17 references. A brief resume of the results of current treatment.

10. "Correlations of Structure and Function and Mechanisms of Recovery in Acute Tubular Necrosis," Oliver, J., *Am. J. Med.*, **15**, 535–57 (1953), 14 references. A magnificent summary based primarily on the author's own work.

11. "Advances in Treatment of Acute and Chronic Renal Insufficiency," Corcoran, A. C., *J. Am. Med. Assoc.*, **153**, 1233–36 (1953), 16 references. Current basic prinicples are summarized in a very useful manner.

DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HEMATOLOGY

1. "Blood: Formed Elements," Dougherty, T. F., and Dougherty, J. H., *Ann. Rev. Physiol.*, **15**, 195–212 (1953), 189 references.

2. "Review of the 1952 Hematology Literature," Wright, C. S., Sundharagiati, B., Bass, J. A., and Bunner, A. E., *Arch. Internal Med.*, **92**, 357–437 (1953), 660 references. An excellent survey of the hematology literature for 1952.

3. "Scandinarian Literature on Haematology in 1951, A Review," Videbaek, A., *Acta Haematol.*, **8**, 387–95 (1952), 78 references.

4. "Scandinavian Literature on Hematology in 1952," Videbaek, A., *Acta Haematol.*, **10**, 267–72 (1953), 76 references. A brief review.

5. "Die Deutschsprachige hämatologische Literatur im Jahre 1951 (unter Ausschluss der Blutgerinnung)," von Begemann, H., and Sievers, K., *Acta Haematol.*, **8**, 173–98 (1952), 344 references.

6. "Die Deutschsprachige hämatologische Literatur im Jahre 1952," von Begemann, H., and Sievers, K., *Acta Haematol.*, **10**, 113–25, 190–207 (1953), 609 references. A review in German of the German hematological literature for 1952.

7. "Physiology and Pathology of Blood Coagulation. A Review of the

Literature of 1951," Koller, F., *Acta Haematol.*, **8**, 81–115, 308–44 (1952), 397 references.

8. "Physiology and Pathology of Blood Coagulation," Koller, F., *Acta Haematol.*, **9**, 257–72, 311–36 (1953), 190 references. The review consists of the references which are well abstracted and systematically arranged.

9. "Clinical Assay of Blood Coagulation Factors," Mann, F. D., *Am. J. Clin. Pathol.*, **23**, 623–37 (1953), 170 references. A brief readable summary of interest to most clinicians.

10. "Mechanism of Blood Coagulation in Normal and Pathological Conditions," Stefanini, M., *Am. J. Med.*, **14**, 64–86 (1953), 106 references. A comprehensive outline.

11. "Factor VII (SPCA): Its Physiopathic Significance," de Nicola, P., *Blood*, **8**, 947–54 (1953), 48 references. Summarization of the available knowledge about the serum prothrombin conversion accelerator, a clotting factor of recent recognition.

12. "Prothrombin and Accessory Factors," Owren, P. A., *Am. J. Med.*, **14**, 201–15 (1953), 55 references. The clinical significance of these factors is well reviewed.

13. "Hemophilia," Quick, A. J., *Am. J. Med.*, **14**,, 349–55 (1953), 14 references. A brief summary of the present status of this ailment.

14. "The Pathological Physiology of Hemorrhagic Conditions," Quick, A. J., *Bull. N. Y. Acad. Med.*, **29**, 226–34 (1953), 5 references. An excellent simplified summary.

15. "The Nature and Treatment of Polycythemia," Lawrence, H. H., Berlin, N. I., and Huff, R. L., *Medicine*, **32**, 323–88 (1953), 137 references. A consideration of the literature on the subject along with a study of 263 patients.

16. "Megaloblastic Anemia of Infancy: Zuelzer, W. W., and Rutzky, J., *Advances in Pediat.*, **6**, 243–306 (1953), 122 references. A thorough clinical review for the hematologist and pediatrician.

17. "Hypoplastic and Apalastic Anemias of Infancy and Childhood," Smith, C. H., *J. Pediat.*, **43**, 457–82 (1953), 94 references. A review of the subject based on personal data and the literature.

18. "Iron Metabolism and the Hypochromic Anemia of Infancy," Josephs, H. W., *Medicine*, **32**, 125–312 (1953), 388 references. An intensive review of the literature supplemented with new data.

19. "Hemolytic Disease of the Newborn," Levine, P., *Advances in Pediat.*, **6**, 97–156 (1953), 173 references. A critical survey of the aspects of immediate interest to the pediatrician.

20. "Differential Diagnosis, Pathogenesis and Treatment of the Thrombocytopenic Purpuras," Lozner, E. L., *Am. J. Med.*, **14**, 459–68 (1953), 58 references. A short review with special regard to the recent literature.

21. "Postoperative Thrombophilia," Warren, R., *New Engl. J. Med.*, **249**, 99–106 (1953), 86 references. An analysis of our present knowledge of postoperative alterations in blood coagulation.

22. "Development of Knowledge Concerning the Gastric Intrinsic Factor and its relation to Pernicious Anemia," Castle, W. B., *New Engl. J. Med.*, **249,** 603–14 (1953), 125 references. A scholarly review by one who had the most to do with the development of our present knowledge of this subject.

23. "Immunohemolytic Mechanisms in Vivo; The Mode of Destruction of Sensitized Red Cells in the Living Organism," Wasatjerna, C. *Blood*, **8,** 1042–51 (1953), 52 references. For the hematologist.

24. "Preservation of Whole Blood and Red Cells," Sloviter, H. A., *Am. J. Med. Sci.*, **225,** 197–204 (1953), 53 references. An evaluation of recent work.

25. "Passage of Molecules Through Capillary Walls," Pappenheimer, J. R., *Physiol. Revs.*, **33,** 387–423 (1953), 165 references. Highly technical but an excellent review for reference purposes.

26. "Disturbances of the Spleen," Wolman, I. J., *Quart. Rev. Pediat.*, **7,** 179–87 (1952), 12 references. A concise survey of the various ailments which concern this organ.

NUTRITION AND NUTRITIONAL DISEASES

1. *Present Knowledge of Nutrition* (Nutrition Foundation, Inc., New York, N. Y., 122 pp., 1953). Based on material which appeared originally in *Nutrition Reviews* which has been revised in the light of current research. An excellent guide.

2. "Supplement to Present Knowledge in Nutrition," *Nutrition Reviews*. **11,** 353–61 (1953). Data from earlier *Nutrition Reviews* which bring the above listed booklet up-to-date. References are primarily to *Nutrition Reviews* where the original literature is cited.

3. "Trends and Needs in Nutrition," Sebrell, W. H., Jr., *J. Am. Med. Assoc.*, **152,** 42–44 (1953). A response to the award of the Joseph Goldberger Award in Clinical Nutrition from the American Medical Association.

4. "Disaster Feeding," Hundley, J. M., *J. Am. Med. Assoc.*, **151,** 1404–8 (1953). A summary of the physiological and psychological factors involved in disaster feeding.

5. "Nutrition of Athletes," Upjohn, H. L., Shea, J. A., Stare, F, J., and Little, L., *J. Am. Med. Assoc.*, **151,** 818–19 (1953), 5 references. A summary of the subject prepared at the request of the Council on Foods and Nutrition of the American Medical Association.

6. "Nutrition and Stress," Mitchell, H. H., *Borden's Rev. Nutrition Research*, **13,** 97–108 (1952), 56 references. A brief review of the relation to stress in man of nutritional deficiencies and the environment.

7. "Nutritional Stress Factors and Food Processing," Lepkovsky, S., *Advances in Food Research*, **4,** 105–32 (1953), 92 references. A provocative review of the possible effects of food processing for storage or consumption and the nature of the diet upon the relation of the food intake to the stress factors as a result of the physiological state, environment, disease, and drugs.

8. "Improving the Quality of Staple Foods," Cowgill, G. R., *Borden's*

Rev. Nutrition Research, **13**, 73–84 (1952), 34 references. Considers enrichment and fortification of foods and hybridization of crops.

9. "Meal Habits and Their Effects on Performance," Hutchinson, R. C., *Nutrition Abstr. & Revs.*, **22**, 283–97 (1952), 100 references. A careful review based on man leading to conclusions which are often discussed but rarely documented.

10. "Nutrition," Hogan, A. G., *Ann. Rev. Biochem.*, **22**, 299–318 (1953), 123 references. A review of the recent literature on the relation of nutrition to congenital malformations.

11. "Nutrition and Resistance to Infection," Schneider, H. A., *Borden's Rev. Nutrition Research*, **14**, 17–32 (1953), 30 references. A short survey of a confused subject.

12. "Water Metabolism," Keith, N. M., *Ann. Rev. Physiol.*, **15**, 63–84 (1953), 138 references.

13. "Kwashiorkor," Williams, C. D., *J. Am. Med. Assoc.*, **153**, 1280–85 (1953). A fine comprehensive review of this tropical nutritional ailment prepared by the leading authority at the request of the Council on Foods and Nutrition of the American Medical Association.

14. "Hypervitaminosis A," Knudson, A. G., and Rothman, P. E., *Am. J. Diseases Children*, **85**, 316–34 (1953), 58 references. A review of hypervitaminosis A with a discussion of this vitamin.

15. "Vitamin E—The Tocopherols," Mattill, H. A., *Borden's Rev. Nutrition Research*, **13**, 109–19 (1952), 48 references. An excellent short summary of the subject.

16. "The Effects of Heat Upon the Nutritive Value of Protein," Rice, E. E., and Beuk, J. F., *Advances in Food Research*, **4**, 233-79 (1953), 161 references.

ENDOCRINOLOGY

1. "Virilism," Jailer, J. W., *Bull. N. Y. Acad. Med.*, **29**, 377–94 (1953), 27 references. The best available review of the subject.

2. "Parathyroid Hormone and Mineral Metabolism," Snapper, I., *Bull N. Y. Acad. Med.*, **29**, 612–24 (1953), 27 references. A brief critical resume

3. "The Pituitary-Adrenal Relationship," Hodges, J. R., *J. Pharm. and Pharmacol.*, **5**, 481-96 (1953), 98 references. A concise critical summary of current knowledge.

4. "The Anterior Pituitary and Adrenal Cortex," Engel, F. L., *Ann. Rev. Physiol.*, **15**, 397–428 (1953), 316 references.

5. "The Three Subtypes of Pituitary Adrenocorticotropin," Wolfson, W. C., *Arch. Internal Med.*, **92**, 108–47 (1953), 49 references. Evidence for the physiological differentiation of adrenocorticotropin (ACTH) into three types.

6. "Cushing's Syndrome," Knowlton, A. I., *Bull. N. Y. Acad. Med*, **29**, 441–65 (1953), 19 references. An excellent personal review.

7. "Management of Addison's Disease in Adrenalectomized Patients,"

Bergenstal, D. M., and Dao, T. L. Y., *Bull. N. Y. Acad. Med.*, **29**, 295–306 (1953), 12 references. A practical description of methods used.

8. "Bilateral Symmetrical Diseases of the Adrenals," Hess, L., *Acta Endocrinol.*, **11**, Suppl. 10, 1–30 (1953), 49 references. A clinical summary.

9. "Corticotropin, Cortisone and Related Steroids in Clinical Medicine: Practical Considerations," Ragan, C., *Bull. N. Y. Acad. Med.*, **29**, 356–76 (1953), 17 references. An excellent brief summary.

10. "Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man," Thorn, G. W. *et al.*, *New Engl. J. Med.*, **248**, 232–45, 284–94, 323–37, 369–78, 414–23, 588–601, 632–46 (1953), 673 references. A thorough scholarly well written review of all aspects of the subject. Of interest to the pharmacologist, endocrinologist, and clinicians in general.

11. "Use of the Steroids and Gonadotropins in Gynecology," Taylor, H. C., Jr., *Bull. N. Y. Acad. Med.*, **29**, 709–24 (1953), no references. A positive practical summary of the subject with no direct reference to the literature.

12. "Biology of the Testes," 17 papers by Nelson, W. O., *et al.*, *Ann. N. Y. Acad. Sci.*, **55**, 543–742 (1952), 235 references. A survey of all points of view in the principal areas of investigation upon male reproduction which are receiving attention at the present time.

13. "Congenital Familial Testicular Deficiency," Sohval, A. R., and Soffer, L. J., *Am. J. Med.*, **14**, 328–48 (1953), 67 references. A clinical review of the condition with reference to the pertinent literature.

14. "Pituitary Thyroid Relationship in Normal and Disordered Thyroid States," Werner, S. C., *Bull. N. Y. Acad. Med.*, **29**, 523–36 (1953), 56 references. A summary in the field of clinical investigation with special reference to Graves disease.

15. "Choice of Management in Patients with Thyrotoxicosis," Sturgis, C. C., *Bull. N. Y. Acad. Med.*, **29**, 537–50 (1953), 9 references. A brief summary of current practices.

16. "Hyperthroidism—An evaluation of Treatment with Antithyroid Drugs Followed by Subtotal Thyroidectomy," Bartels, E. C., *Ann. Internal Med.*, **37**, 1123–34 (1952), 14 references. A review based on a series of 2400 patients treated over nine years.

17. "Prognosis of Hyperthyroidism Treated by Antithyroid Drugs," Solomon, D. H., Beck, J. C., Vanderlaan, W. P., and Astwood, E. B., *J. Am. Med. Assoc.*, **152**, 201–5 (1953)

18. "Thyroiditis and Myxedema," Barr, D. P., *Bull. N. Y. Acad. Med.*, **29**, 551–69 (1953), 40 references. A summary of personal experience.

19. "Thymus," Keynes, G., *Ann. Roy. Coll. Surg. England*, **12**, 88–95 (1953), 15 references. A brief summary of the thymus in relation to its surgery and myasthenia gravis.

DISEASES OF METABOLISM

1. "Current Concepts of Diabetes," Sherry, S., *Bull. N. Y. Acad. Med.*, **29**, 202–25 (1953), 34 references. A recapitulation of current views which stresses our conception of the disease state.

2. "Basic Principles in the Therapy of Diabetes," Ricketts, H. T., *Ann. Internal Med.*, **37**, 1181–87 (1952), 30 references. A truly concise summary.

3. "Electrolyte Metabolism in Diabetic Acidosis," Sprague, R. G., and Power, M. H., *J. Am. Med. Assoc.*, **151**, 970–76 (1953), 12 references. A good summary of the theoretical and practical aspects.

4. "Endocrine Regulation of the Blood Sugar," Conn, J. W., *Ann. Internal Med.*, **38**, 179–87 (1953), 12 references. Most of the literature of investigators which is ready for the clinician is briefly summarized.

5. "Metabolic Effects of Insulin," Stetten, D. W., *Bull. N. Y. Acad. Med.*, **29**, 466–76 (1953), 21 references. A good summary for the metabolism expert.

6. "The relation of Lean Body Weight to Metabolism and Some Consequent Systematizations," Behnke, A. R., *Ann. N. Y. Acad. Sci.*, **56**, 1097–1142 (1953), 59 references.

7. "Physical Medicine and Obesity," Krusen, F. H., *J. Am. Med. Assoc.*, **151**, 296–79 (1953), 3 references. A synopsis of the subject prepared for the Council on Foods and Nutrition of the American Medical Association.

8. "Current Principles of Management in Gout," Gutman, A. B., and Yu, T. F., *Am. J. Med.*, **13**, 744–59 (1952), 40 references. Present knowledge is well reviewed and supplemented by a summary of the author's extensive experience.

9. "Current Therapy of Gout," Smyth, C. J., *J. Am. Med. Assoc.*, **152**, 1106–9 (1953). A resume of the new methods.

10. "The Endocrine Control of Metabolism," Engel, F. L., *Bull. N. Y. Acad. Med.*, **29**, 175–210 (1953), 39 references. An excellent comprehensive review.

11. "Body Fat in Adult Man," Keys, A., and Brozek, J., *Physiol. Rev.*, **33**, 245–325 (1953), 298 references. A complete review of the literature and the subject most useful for reference purposes.

12. "The Lipoidoses," Van Creveld, S., *Advances in Pediat.*, **6**, 190–242 (1953), 247 references. A clinical survey of Xanthomatosis, Gaucher's, Niemann-Pick's, and Tay-Sachs' disease.

13. "Weber-Christian Syndrome," Beerman, H., *Am. J. Med. Sci.*, **225**, 446-62 (1953), 93 references. An excellent critical review of this disturbance in the adipose tissue.

14. "Recent Advances in Potassium Metabolism," Nadler, C. S., *Am. J. Med. Sci.*, **226**, 88–103 (1953), 131 references. A good discussion of certain aspects of the subject.

15. "Potassium Imbalance," Mudge, G. H., *Bull. N. Y. Acad. Med.*, **29**, 846–64 (1953), 40 references. An excellent summary.

16. "The Low Sodium Syndrome: Its Origins and Varieties," Leiter, L., Weston, R. E., and Grossman, J., *Bull. N. Y. Acad. Med.*, **29**, 833–45 (1953), 52 references. A brief outline which covers all aspects of the subject.

17. "Physiology of Calcium Metabolism," Nicolaysen, R., Eeg-Larsen, N., and Malm, O. J., *Physiol. Revs.*, **33**, 424–44 (1953), 126 references. A reference review for the biochemist and nutritionist.

18. "Recent Developments in the Practical Application of Enzymes to Clinical Medicine," Tagnon, H. J., *New Engl. J. Med.*, **249**, 650–57 (1953), 80 references. A new field which is developing slowly.

19. "Serum Cholinesterase in Health and Disease," Vorhaus, L. J., and Kark R. M. *Am. J. Med.*, **14**, 707–19 (1953), 96 references. Levels are described in normal and diseased states and the nature and function of the enzyme discussed.

20. "Lipid Metabolism," Artom, C., *Ann. Rev. Biochem.*, **22**, 211–32 (1953), 178 references. A critical evaluation of the more important work published in 1952.

21. "Carbohydrate Metabolism," Leloir, L. F., and Cardini, C. E., *Ann. Rev. Biochem.*, **22**, 179–210 (1953), 218 references. A nice review of the 1952 literature.

22. "Aminoaciduria in Childhood: Cystinuria and Cystinosis," Eberlein, W. R., *Am. J. Med. Sci.*, **225**, 677–86 (1953), 72 references. A review of the new knowledge in this field.

23. "Metabolism of Amino Acids and Proteins," Christensen, H. N., *Ann. Rev. Biochem.*, **22**, 233–60 (1953), 286 references. Recent literature with special emphasis on protein synthesis.

24. "Metabolism of Phenylalanine and Tyrosine," Lerner, A. B., *Advances in Enzymol.*, **14**, 73–128 (1953), 213 references. A highly technical review of interest to the biochemist and metabolism specialists.

25. "Physiology of the D-Amino Acids," Berg, C. P., *Physiol, Rev.*, **33**, 145–89 (1953), 380 references. Nonclinical.

26. "Occurrence & Significance of Citric Acid in the Animal Organism," Thunberg, T., *Physiol., Revs.* **33**, 1–12 (1953), 72 references. For the biochemist.

27. "Antimetabolites: A Review", Shaw, E., *Metabolism, Clin. and Exptl.*, **2**, 103–19 (1953), 77 references. The various types of antimetabolite action are reviewed.

ALLERGY

1. "A Current Bibliography on Allergy," compiled by Forman, J., *Quart. Rev. Allergy and Appl. Immunol.*, **7**, 83–127, 220–47, 359–94 (1953), 1910 references. Unabstracted references are carefully classified.

2. "The Immunological Response," Haurowitz, F., *Ann. Rev. Microbiol.*, **7**, 389–414 (1953), 252 references.

3. "The Immunologic Aspects of Allergic Conditions," Spain, W. C., *Ann. Internal Med.*, **38**, 188–98 (1953), 43 references. A sound brief discussion with a suitable interest for any field of medicine.

4. "The Cellular Fate of Injected Antigens," Coons, A. H., *Symposia Soc. Exptl. Biol.*, **6**, 166–72 (1952), 22 references.

5. "Immunopolysaccharides," Tomcsik, J., *Ann. Rev. Biochem.*, **22**, 351–70 (1953), 148 references. A short survey of the most important recent contributions from the biochemical and biological aspects.

6. "Allergic Reactions to Bee and Wasp Stings," Mueller, H. L., and Hill, L. W., *New Engl. J. Med.*, **249**, 726–31 (1953), 23 references. The practical aspects of the problem are emphasized.

7. "Phychosomatic Allergy and Its Management," Abramson, H. A., *Quart. Rev. Allergy and Appl. Immunol.*, **7**, 197–219 (1953), 70 references. A review of relevant papers published in English during recent years discussed in the light of the author's personal experience.

8. "Drug Allergy," Brown, E. A., *Quart. Rev. Allergy and Appl. Immunol.*, **7**, 51–82 (1953), 223 references. A review designed for the general practitioner.

9. "Diarrhea of Allergic Origin," Rothman, P., *Am. J. Diseases Children*, **86**, 201–10 (1953), 37 references. A careful consideration of the information about an often questionable diagnosis.

10. "Allergic Purpura, Including Purpura Due to Foods, Drugs and Infections," Ackroyd, J. F., *Am. J. Med.*, **14**, 605–32 (1953), 213 references. An excellent review of this field.

11. "The Phenobarbital Sensitivity Syndrome," McGeachy, T. E., and Bloomer, W. E., *Am. J. Med.*, **14**, 600–4 (1953), 12 references. A careful review of a rare ailment.

12. "ACTH in Reiter's Syndrome," Larson, E., and Zoeckler, S. J., *Am. J. Med.*, **14**, 307–17 (1953), 33 references. A review of the literature and four new cases.

13. "A Study of 23 Cases of Reiter's Syndrome," Hall, W. H., and Finegold, S., *Ann. Internal Med.*, **39**, 533–50 (1953), 20 references. A review of the author's data.

Neoplastic Diseases

1. "The Chemistry of Neoplastic Tissue" Kensler, C. J., and Petermann, M. L., *Ann. Rev. Biochem.*, **22**, 319–40 (1953), 222 references. Recent literature bearing on animal tumors.

2. "Viruses as Causative Agents in Cancer," 33 papers by Rhoads, C. P., *et al.*, *Ann. N. Y. Acad. Sci.*, **54**, 869–1232 (1952), 871 references. A complete review of the current status of virus work in relation to cancer.

3. "Hormonal Control of Neoplastic Growth," Rawson, R. W., *Bull. N. Y. Acad. Med.*, **29**, 595–611 (1953), 83 references. A review of the subject at the moment having mostly to do with studies in experimental animals.

4. "Nutrition in Relation to Cancer," Tannenbaum, A., and Silverstone, H., *Advances in Cancer Research*, **1**, 451–501 (1953), 158 references. A complete, even historical, review of the subject.

5. "Plasma Proteins in Cancer," Winzler, R. J., *Advances in Cancer Research*, **1**, 503–48 (1953), 253 references.

6. "Melanoma," Johnson, P., *Stanford Med. Bull.*, **11**, 33–7 (1953), 35 references. A short statistical summary of 20 cases.

7. "Malignant Melanomas: 92 Cases Treated at the University of Minnesota Hospitals since January 1, 1932," Stewart, D. E., Hay, L. J., and

Varco, R. L., *Intern. Abstr. Surg.*, **97**, 209–27 (1953), 73 references. The general subject is briefly reviewed and 92 cases occurring in the author's institution since 1932 are considered in greater detail.

8. "New Growths of the Pancreas," Smith, R., *Ann. Roy. Coll. Surg. England*, **12**, 366–90 (1953), 15 references. A summary of occurrence and surgical techniques of removal.

9. "Diverticulitis of the Colon Complicated by Carcinoma," Rowe, R. J., and Kollmar, G. H., *Intern. Abstr. Surg.*, **94**, 1–9 (1953), 53 references. A review of all the English literature prior to 1950 pointed up with a consideration of new cases.

10. "Malignant Disease of the Urinary Bladder," Hollands, J. G., *Ann. Roy. Coll. Surg.*, *England*, **11**, 265–86 (1952), 37 references. A brief summary of the subject.

11. "Malignant Thymoma in Myasthenia Gravis," Katz, J. H., *New Engl. J. Med.*, **248**, 1059–61 (1953), 59 references. A brief discussion of the role of the thymus in this disease.

12. "Rhabdomyosarcoma of Skeletal Muscle," Pack, G. T., and Eberhart, W. F., *Surgery*, **32**, 1023–64 (1952), 45 references. A review based primarily on 100 cases observed between 1929 to 1949.

13. "Primary Carcinoma of the Lung," De Bakey, M. E., Ochsner, A., and DeCamp. P. T., *Surgery*, **32**, 877–91 (1952), 103 references. A critical well-documented discussion.

14. "Bronchial Carcinoma: Incidence and Aetiology," Doll, R., *Brit. Med. J.*, **II**, 521–27, 585–95 (1953), 85 references. A critical review of all aspects of the subject.

15. "Facts and Fancies about Cancer of the Lung," Smithers, D. W., *Brit. Med. J.*, **I**, 1235–39 (1953), 17 references.

16. "Effects of Intensive Sex Steroid Hormone Therapy in Advanced Breast Cancer," Kennedy, B. J., and Nathanson, I. T., *J. Am. Med. Assoc.*, **152**, 1135–41 (1953). A statistical analysis of a large series prepared as a special report to the Council on Pharmacy and Chemistry of the American Medical Association.

17. "The Surgical Treatment of Breast Cancer," Lewison, E. F., *Surgery*, **34**, 904–53 (1953), 99 references. An historical and collective review.

18. "A Review of the Influence of Bacterial Infection and of Bacterial Products (Coley's Toxins) on Malignant Tumors in Man," Nants, H. C., Fowler, G. A., and Bogatko, F. H., *Acta Med. Scand.*, **145**, Suppl. 276, 1–103 (1953), 116 references. A critical analysis of the literature and 30 new cases.

19. "Review of 4125 Biopsies of the Cervix with Relation to Carcinoma in Situ," Hoffman, J., and Hahn, G. A., *J. Am. Med. Assoc.*, **151**, 535–40 (1953), 10 references.

20. "Lymphosarcoma in Childhood," Dargeon, H. W., *Advances in Pediat.*, **6**, 13–32 (1953), 31 references. A clinical review of the subject.

21. "Childhood Cancer (Tumors, Leukemia, and Hodgkin's Disease)," Bufkin, J. H., and Davison, W. C., *J. Pediat.*, **42**, 612–32 (1953), 135 references. A brief coverage of the recent literature.

22. "Changing Concepts in the Surgery of Cancer," Dunphy, J. E., *New Engl. J. Med.*, **249**, 17–24 (1953), 75 references.

23. "Epidermal Carcinogenesis," Cowdry, E. V., *Advances in Cancer Research*, **1**, 57–101 (1953), 111 references. A comprehensive review of the subject and literature from an experimental point of view.

24. "The Milk Agent in the Origin of Mammary Tumors in Mice," Dmochowski, L., *Advances in Cancer Research*, **1**, 103–72 (1953), 548 references. A review of the experimental evidence to date.

25. "Hormonal Aspects of Experimental Tumorigenesis," Gardner, W. U., *Advances Cancer Research*, **1**, 173–232 (1953), 359 references. A review of the literature on a lively subject.

Diseases of the Nervous System

1. "Neuro-Anatomy," Crosby, E., and Woodburne, R. T., *Progr. Neurol. and Psychiat.*, **8**, 1–13 (1953), 106 references. A review of the literature of 1952.

2. "General Neurophysiology (Biochemical Aspects)," Himwich, H. E., *Progr. Neurol. and Psychiat.*, **8**, 14–39 (1953), 205 references. An excellent survey of the recent literature.

3. "Regional Physiology of the Central Nervous System," Hoff, E. C., & Wiese, W., *Prog. Neurol. and Psychiat.*, **8**, 40–56 (1953), 60 references.

4. "Somatic Functions of the Central Nervous System," Fulton, J. F., *Ann. Rev. Physiol.*, **15**, 305–28 (1953), 133 references.

5. "Visceral Functions of the Nervous System," Wang, S. C., *Ann. Rev. Physiol.*, **15**, 329–56 (1953), 200 references.

6. "Excitation and Conduction in the Nervous System," Larrabee, M. G. and Edwards, C., *Ann. Rev. Physiol.*, **15**, 283–304 (1953), 183 references.

7. "Electrical Activity of the Brain," Kaada, B. R., *Ann. Rev. Physiol.*, **15**, 39–62 (1953), 265 references. A review of about one fifth of the papers which appeared in the literature during the two years preceding June, 1952.

8. "Special Senses: Thermal Recptors," Zotterman, Y., *Ann. Rev. Physiol.*, **15**, 357–72 (1953), 66 references.

9. "The Autonomic Nervous System," Richius, C. A., and Kuntz, A., *Progr. Neurol. and Psychiat.*, **8**, 197–227 (1953), 383 references.

10. "Physiology of the Circulation of the Brain: An Annotated Bibliography, 1938–1948," Kenk, R., and Nall, M. L., *Physiol. Revs.*, **32**, Suppl. 1, 1–437 (1952), 2268 references.

11. "Biologic Transducers," Davis, H., *Federation Proc.*, **12**, 661–72 (1953), 34 references. A provocative discussion bearing on the "dimensions" of vision and hearing.

12. "Pharmacology of the Nervous System," Marrazzi, A. S., and Hart, E. R., *Progr. Neurol. and Psychiat.*, **8**, 69–88 (1953), 130 references.

13. "Neuropathology," Ferraro, A., and Roisin, L., *Progr. Neurol. and Psychiat.*, **8**, 57–68 (1953), 44 references. A review of the more important literature of 1952.

14. "Clinical Neurology," Yaskin, J. C., and Rupp, C., *Progr. Neurol.*

and Psychiat., **8**, 89–155 (1953), 207 references. An excellent review of current developments.

15. "Cerebral Swelling: Its Physiology, Pathology, Clinical Symptoms and Signs, Differential Diagnosis and Treatment," Atkinson, W. J., *Ann. Roy. Coll. Surg. England*, **11**, 367–94 (1952), 22 references. A brief review of a subject of much importance to the neurosurgeon.

16. "Recent Advances in the Knowledge of the Mechanism, Diagnosis and Treatment of Head Injury," Gurdjian, E. S., *Am J.. Med. Sci.*, **226**, 214–20 (1953), 38 references. A review of advances made during the past decade.

17. "Cerebral Trauma and Traumatic Infection of the Central Nervous System," Wycis, H. T., *Progr. Neurol. and Psychiat.*, **8**, 333–40 (1953), 42 references.

18. "Tension Headache," Friedman, A. P., Pool, N. d. S., and von Storch, T. J. C., *J. Am. Med. Assoc.*, **151**, 174–77 (1953), 7 references.

19. "Infectious Neuronitis, Present Concepts of Etiology and Treatment," Von Hagen, K. O., and Baker, R. N., *J. Am. Med. Assoc.*, **151**, 1465–72 (1953), 12 references. A brief review of the Guillain-Barre symptom complex.

20. "The Surgical Treatment of Pain and Motor Disorders," Walker, E. A., and Warner, W. A., *Progr. Neurol. and Psychiat.*, **8**, 363–73 (1953), 66 references.

21. "Surgery of the Spinal Cord and Column," Scott, M., *Progr. Neurol. and Psychiat.*, **8**, 323–32 (1953), 36 references.

22. "Brain Tumors," Nihlein, A., *Progr. Neurol. and Psychiat.*, **8**, 341–62 (1953), 100 references.

23. "The Cervical Disc Syndrome: Differential Diagnosis & Management based on 26 Operated Cases," Pool, J. L., *Bull. N. Y. Acad. Med.*, **29**, 47–59 (1953), 27 references. A clinical summary.

24. "Cervical Ribs," Ray, B. S., Hardy, R., and Parsons, H., *Bull. N. Y. Acad. Med.*, **29**, 60–70 (1953), 30 references. A review analyzing a large series of operative cases.

25. "Neuroblastoma," Phillips, R., *Ann. Roy. Coll. Surg. England*, **12**, 29–48 (1953), 47 references. A clinical resume.

26. "Present Status of Surgical Treatment of Meniere's Disease," Neffson, A. H., *Am. J. Med. Sci.*, **226**, 442–63 (1953), 84 references. A comprehensive review.

27. "Peripheral Nerve Surgery," Woodhall, B., *Progr. Neurol. and Psychiat.*, **8**, 317–22 (1953), 23 references.

28. "Affections of the Facial Nerve," Lathrop, F. D., *Bull. N. Y. Acad. Med.*, **28**, 797–808 (1953), 30 references. A brief discussion of various affections of the facial nerve.

29. "Medicolegal Implications of Paralysis of the Recurrent Laryngeal Nerve," Rose, D. E., *Am. J. Surg.*, **85**, 729–37 (1953), 21 references. An outline review of the subject.

Psychiatry and Clinical Psychology

1. "Higher Functions of the Nervous System," Harlow, H. F., *Ann. Rev. Physiol.*, **15**, 493–514 (1953), 53 references.

2. "Child Psychology," Harris, D. B., *Ann. Rev. Psychol.*, **4**, 1–30 (1953), 160 references.

3. "Vision," Vernon, M. D., *Ann. Rev Psychol.*, **4**, 59–88 (1953), 154 references. A review of recent developments in the psychological aspects of sight.

4. "Hearing," Licklider, J. C. R., *Ann. Rev. Psychol.*, **4**, 89–110 (1953), 92 references. A survey of the recent contributions to the psychology or subjective attributes of hearing.

5. "Somesthesis and the Chemical Senses," Ruch, T. C., *Ann. Rev. Physiol.*, **4**, 111–36 (1953), 61 references. A review of the current literature on the mechanoreceptors, propioceptors, cold and pain receptors, visceral and deep sensation, olfaction and taste.

6. "Individual Differences," Anastasi, A. *Ann. Rev. Psychol.*, **4**, 137–56 (1953), 139 references.

7. "Personality," Bronfenbrenner, U., *Ann. Rev. Psychol.*, **4**, 157–82 (1953), 111 references. Current personality theory.

8. "Social Psychology and Group Processes," Newcomb, T. N., *Ann. Rev. Psychol.*, **4**, 183–214 (1953), 117 references.

9. "Industrial Psychology," Harrell, T. W., *Ann. Rev. Psychol.*, **4**, 215–38 (1953), 140 references.

10. "Physiological Psychology," Neff, W. D., *Ann. Rev. Psychol.*, **4**, 255–72 (1953), 107 references.

11. "Abnormalities of Behavior," White, R. W., *Ann. Rev. Psychol.*, **4**, 273–94 (1953), 75 references.

12. "Clinical Methods: Psychodiagnostics," Rotter, J. B., *Ann. Rev. Psychol.*, **4**, 295–316 (1953), 115 references. Recent diagnostic tests.

13. "Testing for Psychological Deficit," Hunt, H. F., *Progr. Clin. Psychol.*, **1**, 91-107 (1952), 89 references.

14. "Thermatic Apperception Test and Other Apperceptive Methods," Bellak, L., *Progr. Clin. Psychol.*, **1**, 149–72 (1952), 61 references.

15. "The Rorschach: Thirty Years After," Hertz, M. R., *Progr. Clin. Psychol.*, **1**, 108–48 (1952), 262 references.

16. "The Szondi Test," Deri, S. K., *Progr. Clin. Psychol.*, **1**, 222–33 (1952), 50 references.

17. "Applications of Clinical Psychology to Assessment," Mackinnon, D. W., *Progr. Clin. Psychol.*, **1**, 425–29 (1952), 37 references.

18. "Clinical Methods: Psychotherapy," Sanford N., *Ann. Rev. Psychol.*, **4**, 317–42 (1953), 68 references. Primarily concerned with recent contributions to group therapy and the treatment of schizophrenia.

19. "Client-Centered Counseling and Psychotherapy," Raskin, N. J., *Progr.Clin. Psychol.*, **1**, 236–48 (1952), 25 references.

20. "Counseling: Therapy and Diagnosis," Williamson, E. G., *Ann. Rev. Psychol.*, **4**, 343–60 (1953), 99 references.

21. "Special Disabilities," Cobb, K., *Ann. Rev. Psychol.*, **4**, 361–86, (1953), 138 references. Psychological problems in relation to vision, hearing, and speech defects.

22. "Educational Psychology," Carter, H. D., *Ann. Rev. Psychol.*, **4**, 387–406 (1953), 129 references.

23. "Applications of Clinical Psychology to Mental Deficiency," Heiser, K. F., *Progr. Clin. Psychol.*, **1**, 450–58 (1952), 46 references.

24. "Applications of Clinical Psychology to Sexual Disorders", Ellis, A., *Progr. Clin. Psychol.*, **1**, 467–80 (1952), 231 references.

25. "Statistical Methods," Kogan, L. S., *Progr. Clin. Psychol*, **1**, 519–35 (1952), 86 references.

26. "Statistical Theory & Research Design," Mosteller, F., *Ann. Rev. Psychol.*, **4**, 407–34 (1953), 84 references.

27. "Review of Neuropsychiatry," Cobb, S., *Arch. Internal Med.*, **92**, 273–82 (1953), 35 references. A detailed critical review of recent literature.

28. "Epilepsy," Forster, F. M., and Berry, R. G., *Progr. Neurol., and Psychiat.*, **8**, 184–96 (1953), 103 references.

29. "Clinical Psychiatry," Simon, A., *Progr. Neurol., and Psychiat.* **8**, 388–435 (1953), 355 references.

30. "Electroencephalograph," Brazier, M. A. B., *Progr. Neurol and Psychiat.*, **8**, 244-63 (1953), 178 references.

31. "Mental Hygiene," Freed, H., *Progr. Neurol. and Psychiat.*, **8**, 436–44 (1953), 65 references.

32. "Criminal Psychology," Maughs, S. B., *Progr. Neurol. and Psychiat.*, **8**, 448–61 (1953), 30 references.

33. "Child Psychiatry," Dubo, S., and Rabinovitch, R. D., *Progr. Neurol. and Psychiat.*, **8**, 462–74 (1953), 48 references.

34. "The Neuroses," Masserman, J. H., and Dushkin, M. A., *Progr. Neurol. and Psychiat.*, **8**, 475–85 (1953), 22 references.

35. "Alcoholism," Allen, E. B., and Prout, C. T., *Progr. Neurol. and Psychiat.*, **8**, 486–94 (1953), 41 references.

36. "Psychiatric Aspects of Drug Addiction," Wickler, A., and Rasor, R. W., *Am. J. Med.*, **14**, 566–70 (1953), 17 references. Brief!

37. "Applications of Clinical Psychology to Addiction," Wilkins, W. S., *Progr. Clin. Psychol.*, **1**, 481–90 (1952), 55 references.

38. "Psychosomatic Medicine," Weiss, E., Saul, L. J., and Lyons, J. W., *Progr. Neurol. and Psychiat.*, **8**, 495–501 (1953), 12 references.

39. "Changing Concepts of Health and Disease, with Particular Reference to 'Psychosomatic Medicine'", Bomford, R. R., *Brit. Med. J.*, **I**, 634–39 (1953), 18 references. A philosophical discussion.

40. "Psychoanalysis," Frank R. L., *Progr. Neurol. and Psychiat.*, **8**, 502–16 (1953), 57 references.

41. "Projective Methods," Bellak, L., and Brower, D., *Progr. Neurol. and Psychiat.*, **8**, 517–39 (1953), 18 references.

42. "Group Psychotherapy," Scheidlinger, I., *Progr. Clin. Psychol.*, **1**, 268–77 (1952), 76 references.

43. "Group Psychotherapy," Slavson, S. R., Hallowitz, E., and Rosenthal, L., *Progr. Neurol. and Psychiat.*, **8**, 527–40 (1953), 57 references.

44. "Psychosurgery," Freeman, W., *Progr. Neurol. and Psychiat.*, **8**, 374–87 (1953), 98 references.

45. "Psychosurgery," Greenblatt, M., and Solomon, H. C., *New Engl. J. Med.*, **248**, 19–27, 59–67 (1953), 196 references. A critical study of the contributions in this field since its reactivation in 1941.

46. "Physiodynamic Therapy (Shock Therapy)" Wilcox, P. H., *Progr. Neurol. and Psychiat.*, **8**, 541–57 (1953), 132 references.

47. "Psychiatric Nursing and Occupational Therapy," Bennett, A. E., and Engle, B., *Progr. Neurol. and Psychiat.*, **8**, 558–67 (1953), 70 references.

48. "Rehabilitation," Marks, M., and Greene, L. B., *Progr. Neurol and Psychiat.*, **8**, 568–75 (1953), 139 references.

49. "Some Recent Contributions in the Field of Geriatric Psychiatry," Silverman, A. J., *Am. J. Med. Sci.*, **225**, 101–6 (1953), 43 references. A brief outline.

50. "A Psychomedical Survey of a Private Outpatient Clinic in a University Hospital," Lewis, B. K., *Am. J. Med.*, **14**, 586–99 (1953), 42 references. A careful study of good data.

Diseases of the Skin

1. "Biochemistry & Physiology of Epidermis," Carruthers, C., and Suntzeff, V., *Physiol. Revs.*, **33**, 229–43 (1953), 136 references. A review which emphasizes the small amount of information we have about the skin.

2. "Nutritional Influences on the Physiology of the Skin: Observations on the Metabolism of Vitamin A." Griesemer, R. D., Frazier, C., and Blank I. H., *Medicine*, **32**, 293–321 (1953), 117 references. A new study integrated with a review of the literature.

3. "Recent Advances in Dermatology," Nelson, C. T., *Bull. N. Y. Acad. Med.*, **29**, 138–49 (1953), 5 references. A short clinical resume.

4. "The Physiology of Sweating," Randall, W. C., *Am. J. Physical Med.*, **32**, 292–318 (1953), 98 references. A review of the subject with special reference to fields in which there has been intensive recent investigation.

5. "Miliaria," Shelley, W. B., *J. Am. Med. Assoc.*, **152**, 670–73 (1953), 7 references. Skin changes associated with obstruction of sweat gland ducts.

6. "The Epidemiology of Some Skin Infections," Cruickshank, R., *Brit. Medical J.*, **I**, 55–59 (1953), 19 references. A brief discussion.

7. "Natural History of Lupus Erythematosus Disseminatus," Jessar, R. A., Lamont–Haynes, R. W., and Ragan, C., *Ann. Internal Med.*, **38**, 717–31 (1953), 59 references. A review based on 44 new cases and 279 from the literature.

8. "Acrodynia and Mercury," Warkany, J., and Hubbard, D. M., *J. Pediat.*, **42**, 365–86 (1953), 97 references. The evidence for an association of

mercury medication or poisoning with the occurence of acrodynia is summarized.

9. "Pemiphigus," Lever, W. F., *Medicine*, **32**, 1–123 (1953), 237 references. A profusely illustrated review of the subject with adequate coverage of the literature.

10. "The Shwartzman Phenomenon," *Brit. J. Dermatol.*, **65**, 389–405 (1953), 81 references. A critical review of its pathogenesis and possible clinical ramifications particularly in relation to dermatological manifestations.

11. "Psychiatric Factors in Dermatologic Disorders," Silverman, A. J., *Am. J. Med. Sci.*, **226**, 104–10 (1953), 42 references. A review in general terms.

12. "Treatment of Melanin Hyperpigmentation," Lerner, A. B., and Fitzpatrick, T. B., *J. Am. Med. Assoc.*, **152**, 577–82 (1953), 10 references.

DISEASES OF THE BONES, JOINTS AND MUSCLES

1. "The Local Physiology of Bone Repair," Wrist, M. R., and McLean, F. C., *Am. J. Surg.*, **85**, 444–49 (1953), 14 references. A brief summary designed as a basis for pathological discussions.

2. "The Storage of Elements in the Skeleton," Duckworth, J., and Hill, R., *Nutrition Abstr. and Revs.*, **23**, 1–17 (1953), 229 references. Of secondary interest to human nutrition.

3. "Common Diseases and Disabilities of the Hand," Psaki, R. C., and Kuitert, J. H., *Am. J. Physical Med.*, **31**, 183–192 (1953), 7 references. A concise review of the subject.

4. "Trauma and Dupuytren's Contracture," Moorhead, J. J., *Am. J. Surg.*, **85**, 352–58 (1953), 37 references. The recent literature on this disputed relationship is critically reviewed.

5. "New Techniques and Materials in Upper-Extremity Prosthetics," Thorndike, A., *New Engl. J. Med.*, **247**, 1022–33 (1952), 14 references. Recent advances are enumerated, described and evaluated.

6. "Rheumatism and Arthritis, Review of American and English literature of Recent Years" (10th Rheum Rev.), Robinson, W. D. *et al. Ann. Internal Med.*, **39**, 498–618, 757–905 (1953), 2274 references. This review is a thorough digest of all aspects of the subject from the literature of 1946 through 1950 by a group of twelve authorities.

7. "Primer on the Rheumatic Diseases," *J. Am. Med. Assoc.*, **152**, 322–31, 405–15, 522–31 (1953), 12 references. A most useful review of the rheumatic diseases in general prepared by a Committee of the American Rheumatism Association.

8. "Pelvo-Spondylitis Ossificans in the Male, and Genito-Urinary Infection," Romanus, R., *Acta Med. Scand.*, **145**, *Suppl.* **280**, 1–368 (1953), 399 references. The etiological significance of the infection based on the literature and 117 new cases.

9. "Problem of Painful Shoulder," Coventry, M. B., *J. Am. Med. Assoc.*, **151**, 177–85 (1953), 27 references. A brief review of the ailment.

10. "Mechanics of Voluntary Muscle," Ralston, H. J., *Am. J. Physical Med.*, **32**, 166–84 (1953), 10 references. The subject itself is reviewed in detail there being a paucity of literature having a direct bearing.

11. "Fundamental Mechanics of Skeletal Muscle Contraction," Sandow, A., *Am. J. Physical Med.*, **31**, 101–25 (1952), 65 references. A review of the fundamental features.

12. "Muscle and Nerve—Physiologic Orientation," Gerard, R. W., and Taylor, R. E., *Am. J. Med.*, **15**, 83–98 (1953), 176 references. Provides a general perspective and a concise discussion of the physiology of muscle contraction.

13. "Innervation of Voluntary Muscle," Tiegs, O. W., *Physiol. Revs.*, **33**, 90–144 (1953), 460 references. An important summary of a complex field.

14. "The Innervation of Skeletal Muscle," Hodes, R., *Ann. Rev. Physiol.*, **15**, 139–64 (1953), 167 references.

15. "Clinical Problems in Neuromuscular Physiology," Denny-Brown, D., *Am. J. Med.*, **15**, 368–90 (1953), 84 references. A lucid exposition of a subject of wide clinical importance.

16. "Some Aspects of the Pharmacology of Neuromuscular Function," Riker, W. F., Jr., *Am. J. Med.*, **15**, 231–49 (1953), 97 references. Neuromuscular function is adequately reviewed in relation to drug action.

17. "Inheritance of Diseases Primary in the Muscles," Stephens, F. E., *Am. J. Med.*, **15**, 558–69 (1953), 53 references. Summarizes a large experience and points up the importance and difficulties of human genetics.

18. "Abnormalities in Neuromuscular Transmission, with Special Reference to Myasthenia Gravis," Grob, D., and Harvey, A. M., *Am. J. Med.*, **15**, 695–709 (1953), 87 references. They review a large experience.

19. "A Historical Review of Myasthenia Gravis from 1672 to 1900," Viets, H. R., *J. Am. Med. Assoc.*, **153**, 1273–80 (1953), 18 references. An excellent summary.

20. "Course and Management of Myasthenia Gravis," Grob, D., *J. Am. Med. Assoc.*, **153**, 529–32 (1953), 11 references. A review of the fate of 202 patients over 34 years.

DISEASES OF THE REPRODUCTIVE SYSTEM

1. "Reproduction," Krohn, P. L., and Zuckerman, S., *Ann. Rev. Physiol.*, **15**, 429–56 (1953), 279 references.

2. "The Premenstrual Syndrome," Greene, R., and Dalton, K., *Brit. Med. J.*, **1**, 1007–14 (1953), 61 references. A critical analysis of the subject.

3. "Changing Indications for Therapeutic Abortion," Russell, K. P., *J. Am. Med. Assoc.*, **151**, 108–11 (1953), 11 references. A twenty year survey.

4. "The Human Ovary in Pregnancy," Nelson, W. W., and Greene, R., *Intern. Abstr. Surg.*, **97**, 1–22 (1953), 62 references. An excellent review based not only on the literature but extensive material collected by the authors.

5. "The Heart in Pregnancy," Rubin, A., *Amer. J. Med. Sci.*, **225**, 687–

99, (1953), 144 references. A short review of the significant contributions since 1941 in the field of maternal cardiovascular physiology and heart disease.

6. "The Hazards of Pregnancy in Women with Heart Disease," Bramwell, C., *Brit. Med. J.*, **1**, 898–901 (1953), 13 references. A very good review of the subject and its current status.

7. "Fetal Mortality in Cesarean Section," Litchfield, H. R., Sternberg, S. D., Halperin, J., and Turin, R., *J. Am. Med. Assoc.*, **151**, 783–85 (1953). A survey of 1000 cases.

8. "Vaginal Hysterectomy," Levi, A. A., *Am. J. Surg.*, **85** 683–90 (1953), 22 references. A survey of new data and a review of the literature designed to emphasize the usefulness of this procedure.

9. "Unnecessary Hysterectomies," Doyle, J. C., *J. Am. Med. Assoc.*, **151**, 360–65 (1953), 3 references. A review of six thousand patients in 35 hospitals.

10. "Functional Disorders of Menstruation in Adolescence," McArthus, J. W., *New Engl. J. Med.*, **249**, 361–67 (1953), 56 references. A useful much needed survey.

11. "Experimental Production of Congenital Anomalies," Ingalls, T. H., Curley, F. J., and Prindle, R. A., *New Engl. J. Med.*, **247**, 758–68 (1952), 43 references. Discussed in relation to the occurrence of congenital anomalies in Man.

RADIOLOGY AND RADIOACTIVITY

1. "Radiology of the Skull and Central Nervous System," Young, B. R., and Scanlan, R. L., *Progr. Neurol. and Psychiat.*, **8**, 300–16 (1953), 65 references.

2. "Pediatric Radiology," Neuhauser, E. B. D., and Wittenborg, M. H., *New Engl. J. Med.*, **249**, 62–68 (1953), 31 references. A promotional review.

3. "An Evaluation of the Use of Radiation in the Treatment of Endometrial Cancer," Arneson, A. N., *Bull. N. Y. Acad. Med.*, **29**, 395–410 (1953), 19 references. A critical consideration which favors this therapy as an accessory procedure.

4. "The Dosimetry of Artificial Radioactive Isotopes," Mayneord, W. V., and Sinclair, W. K., *Biol. and Med. Physics*, **3**, 1–63 (1953), 118 references. A comprehensive review of the considerations determining diagnostic and therapeutic use of isotope radiation in the individual patient.

5. "Radiation Protection Comes of Age," Chamberlain, R. H., *J. Am. Med. Assoc.*, **153**, 488–91 (1953), 8 references. A critical discussion of the subject.

6. "Protective Mechanisms in Ionizing Radiation Injury," Patt, H. M., *Physiol. Revs.*, **33**, 35–76 (1953), 377 references. For the biochemist and physiologist.

7. "Fundamental Aspects of Radiation Protection From a Microbiological Point of View," Hollaender, A., and Stapleton, G. E., *Physiol. Revs.*, **33**, 77–89 (1953), 53 references.

8. "Biochemical Aspects of the Radiation Syndrome," Ord, M. G., and

Stocken, L. A., *Physiol. Revs.*, **33**, 356–86 (1953), 274 references. An excellent summary of the subject, including a list of methods and compounds used to combat radiation damage.

9. "Effects of Radiations on Biological Systems," Sparrow, A. H. and Rubin, B. A., *Biol. Progress*, **2**, 1–52 (1952), 225 references.

DISEASES OF THE EYE

1. "Physiology of Vision," Chang, H. T., *Am. Rev. Physiol.*, **15**, 373–96 (1953), 199 references.

2. "The Biochemistry of Vision," Wald, G., *Ann. Rev. Biochem.*, **22**, 497–526 (1953), 123 references.

3. "Physiologic Chemistry of the Eye," von Sallmann, L., *Arch. Ophthalmol.*, **50**, 514–39 (1953), 100 references. A review of the papers published during 1952.

4. "Optics and Visual Physiology," Ogle, K. N., *Arch Ophthalmol.*, **50**, 81–108 (1953), 181 references. A fine summary of recent developments.

5. "Vision," Wald, G., *Federation Proc.*, **12**, 606–11 (1953), 25 references. A review of the retinal pigments for the physiologist and some opthalmologists.

6. "Pharmacology and Toxicology," Harris, J. E., *Arch. Ophthalmol.*, **50**, 192–247 (1953), 372 references. An extensive review with particular reference to opthalmology covering the literature of 1952–53.

7. "Lids, Lacrimal Apparatus, and Conjunctiva," Allen, J. H., *Arch. Ophthalmol.*, **49**, 90–109 (1953), 180 references. Systematic review of recent literature.

8. "Cornea and Sclera," Berliner, M. L., *Arch. Ophthalmol.*, **49**, 22–36 (1953), 131 references. A review of pertinent literature from October 1951–52.

9. "Strabismus," Wheeler, M. C., *Arch. Ophthalmol.*, **50**, 109–22 (1953), 54 references. The significant publications in 1952 pertaining to this subject are well covered.

10. "The Orbit," DeVoe, A. G., *Arch Opthalmol.*, **50**, 375–95 (1953), 119 references. A careful review of the literature for 1952.

11. "Diseases of the Uveal Tract," Hogan, M. J., *Arch. Ophthalmol.*, **49**, 324–63 (1953), 139 references. The important features of this subject are reviewed for the October 1951–52 literature.

12. "Aqueous Veins," Ascher, K. W., *Arch Ophthalmol.* **49**, 438–48 (1953), 80 references. A review of their status based on the literature of the eleven years since their description.

13. "Diseases of the Retina," Maumenee, A. E., *Arch. Ophthalmol.*, **49**, 553–86, 675–710 (1953), 255 references. A critical and detailed review covering the recent literature.

14. "The Electroretinogram," Bounds, Q. W., *Arch. Ophthalmol.*, **49**, 63–89 (1953), 74 references. A rather complete review of the subject and past literature.

15. "Retinal Micro-Aneurysms," Wagener, H. P., *Am. J. Med. Sci.*, **225**, 205–20 (1953), 51 references. A critical consideration with special reference to diabetic retinopathy.

16. "Radiation Cataract," Ham, W. T., Jr., *Arch. Ophthalmol.*, **50**, 618–43 (1953), 135 references. A review of all available literature covering Japanese atom bomb victims, accidental nuclear-reaction victims as well as experimental work.

17. "Glaucoma," Scheie, H. G., *Arch. Ophthalmol.*, **48**, 752–82 (1953), 149 references. A well-organized review of the literature for 1951-52.

18. "Neuro-Ophthalmology," Bender, M. B., and Bergman, P. J., *Progr. Neurol. and Psychiat.*, **164**–83 (1953), 101 references.

19. "Ophthalmologic Diagnosis of Meningiomas of the Sphenoidal Ridge," Kearns, T. R., *Am. J. Med. Sci.*, **226**, 221–28 (1953), 13 references. A review of the more recent literature and 106 additional cases.

DISEASES OF THE EAR, NOSE, AND THROAT

1. "Otoneurology," Perlman, H. B., and Lindsay, J. R., *Progr. Neurol. and Psychiat.*, **8**, 156–63 (1953), 34 references.

2. "Functional Examination of Hearing," Lewy, A., Shapiro, S. L., and Leshin, N., *Arch. Otolaryngol.*, **58**, 205–32, (1953), 84 references. A critical review of current pertinent literature.

3. "Otosclerosis," Fowler, E. P., *Arch. Otolaryngol.*, **57**, 334–63 (1953), 114 abstracts. Indexed abstracts of the literature for 1950-51.

4. "Chronic Progressive Deafness, including Otosclerosis and Diseases of the Inner Ear," Juers, A. L., Derlacki, E. L., and Shambaugh, G. E., *Arch. Otolaryngol.*, **57**, 87–104 (1953), 64 references. Summaries of bibliographic material available for 1950.

5. "Otitis Media and Complications," Dysart, B. R., *Arch. Otolaryngol.*, **5**, 211–21 (1953), 34 references. Summaries of the literature for 1951.

6. "Studies of Syphilis of the Ear and Penicillin," Ittkin, P., *Am. J. Med. Sci.*, **225**, 427–45 (1953), 73 references. The punch line of this review is the conclusion that penicillin will cause syphilis of the inner ear and eighth nerve to soon decline to an insignificant level.

7. "The Surgery of the Temporal Bone," Cawthorne, T., *Ann. Roy. Coll. Surg. England*, **12**, 403–23 (1953), 59 references. A review of an area (suppurative ear disease) in which there is decreasing surgical intervention.

8. "The Paranasal Sinuses," Salinger, S., *Arch. Otolaryngol.*, **58**, 313–58 (1953), 153 references. A survey of the recent literature through 1951.

9. "Tonsils and Adenoids," Adin, L. E., and Singleton, J. D., *Arch. Otolaryngol.*, **57**, 686–704 (1953), 41 references. Summaries of the literature for 1951.

10. "Tumors of the Nose and Throat," Figi, F. A., and Devine, K. D., *Arch. Otolaryngol*, **56**, 535–55, 644–62 (1952), 213 references. A thorough review of the more recent literature.

11. "Plastic Surgery during the Year 1951," Peer, L. A., and Walker, J. C., *Arch. Otolaryngol.*, **57**, 525–61 (1953), 174 references.

Laboratory Aids to Diagnosis and Therapy

1. "Protein Flocculation Reactions," Saifer, A., *Am. J. Med.*, **13**, 730–43 (1952), 121 references. A review stressing a physicochemical approach in attempting to elucidate the various liver function tests., etc.

2. "Cerebrospinal Fluid," Spiegel-Adolf, M., *Progr. Neurol. and Psychiat.*, **8**, 283–99 (1953), 157 references.

3. "Exfoliative Cytology as a Screen Test for Urinary Tract Malignancy," Silberblatt, J. M., *Bull. N. Y. Acad. Med.*, **29**, 889–97 (1953), 9 references. An examination of a new diagnostic method.

4. "The Treponemal Immobilation Test," Beerman, H., *Am. J. Med. Sci.*, **226**, 425–41 (1953), 85 references. A detailed examination of all literature bearing on this test.

Therapeutics and Toxicology

1. "Bacterial Resistance as a Factor in Antibotic Therapy," Long, P. H., *Bull. N. Y. Acad. Med.*, **28**, 809–16 (1953), 19 references. A short consideration of an important practical matter.

2. "Choice of An Antibiotic," Karelitz, S., *J. Pediat.*, **42**, 478–504 (1953), 131 references. An interpretive review of general clinical interest.

3. "Use of Antibiotics in Tropical Diseases," 33 papers by H. W. Brown and 50 other authors, *Ann. N. Y. Acad. Sci.*, **55**, 967–1284, (1952), 752 references. A symposium which summarizes and brings up-to-date this broad field.

4. "Recent Developments in Pharmacy of Antibiotics," Woodard, W. A., *J. Pharm. Pharmacol*, **4**, 1009–36 (1952), 87 references. An excellent treatise for anyone concerned with antibiotic preparations.

5. "Antibiotic Synergism and Antagonism: An Assessment of the Problem," Jawetz, E., and Gunnison, J. B., *Pharmacol. Revs.*, **5**, 175–92 (1953), 99 references. A timely review of a problem of much research as well as clinical interest intended of course for the bacteriologist and clinical investigator.

6. "Symposium on the Mode of Action of Antibiotics," Wyss, O., Smith, G. M., Hobby, G. L., Oginsky, E. L., and Pratt, R., *Bact. Revs.*, **17**, 17–49 (1953), 102 references. For the bacteriologist and clinical investigator.

7. "Biochemistry of Antibiotics," Duggar, B. M., and Singleton, V. L., *Ann. Rev. Biochem.*, **22**, 459–96 (1953), 288 references.

8. "Antibiotics," Heilman, F. R., *Ann. Rev. Microbiol.*, **7**, 219–44 (1953), 261 references.

9. "Clinical Uses of Currently Available Antibiotics," Finland, M., *Brit. Med. J.*, **II**, 1115–21 (1953), no references. An excellent critical summary of general interest.

10. "Drug Treatment of Hypertension," Hoobler, S. W., and Dontas, A. S., *Pharmacol. Revs.*, **5**, 135–74 (1953), 299 references. A good review of a lively field.

11. "Excitatory & Anti-Curare Properties of Acetylcholine and Related

Quaternary Ammonium Compounds at the Neuromuscular Junction,"
Riker, W. F., Jr., *Pharmacol. Revs.*, **5**, 1–86 (1953), 271 references. A complete highly technical review for the pharmacologist and physiologist.

12. "Effects and Treatment of Nerve Gas Poisoning," Grob, D., and Harvey, A. M., *Am. J. Med.*, **14**, 52–63 (1953), 10 references. A review of some of the newer, more toxic organic phosphate anticholinesterase compounds.

13. Pharmacology of Drugs Affecting Skeletal Muscle," Randall, L. O., and Jampolsky, L. M., *Am. J. Physical Med.*, **32**, 102–125 (1953), 110 references. A clear concise review of the subject.

14. "Clinical Characteristics of Addictions," Isbell, H., and White, W. M., *Am. J. Med.*, **14**, 558–65 (1953), 13 references. A most useful summary for any clinician.

15. "The Phenomena of Tolerance," Seevers, M. H., and Woods, L. A., *Am. J. Med.*, **14**, 546–57 (1953), 46 references. A bare outline of a new and reasonable hypothesis.

16. "The Chemistry of Drugs of Addiction," May, E. L., *Am. J. Med.*, **14**, 540–45 (1953), 36 references. An analysis of structure and action relationship.

17. "Treatment of Drug Addiction," Fraser, H. F., and Grider, J. A., Jr., *Am. J. Med.*, **14**, 571–77 (1953), 19 references. A practical outline.

18. "Combined Chemotherapy in Bacterial Infections," Garrod, L. P., *Brit. Med. J.*, **I**, 953–57 (1953), 51 references. A general review of the subject.

19. "An Evaluation of Anticoagulant Therapy," Wright, I. S., *Am. J. Med.*, **14**, 720–30 (1953), 50 references. A critical consideration of various agents.

20. "Toxic Reactions Due to Intravenous Iron," Librach, I. M., *Brit. Med. J.*, **I**, 21–24 (1953), 29 references. The causation of iron intoxication is reviewed in the light of two further cases.

21. "Some Recent Advances in the Pharmacology of Salicylates," Smith, M. J. H., *J. Pharm. Pharmacol.*, **5**, 81–93 (1953), 73 references. A review which stresses the recent literature but illustrates the many unsolved problems in the pharmacology of this well-known drug.

22. "Mechanism of Corticosteroid Action in Disease," 23 papers by O. Hechter and 48 other authors, *Ann. N. Y. Acad. Sci.*, **56**, 623–814 (1953), 546 references. A search for information through a symposium devoted to relevant biochemical and physiological investigations.

23. "Clinical and Hematologic Effects of Triethylene Melamine," Axelrod, A. R., Berman, L., and Murphy, R. V., *Am. J. Med.*, **15**, 684–94 (1953), 51 references. A concise informative review on the use of this agent in malignancies and particularly Hodgkin's disease and polycythemia vera.

24. "Ion Exchange Resins in Medicine and Biological Research," *Ann. N. Y. Acad. Sci.*, **57**, 61–323 (1953), 501 references. A symposium of 20 articles by 33 authors.

25. "Hypoplastic Anemias and Related Syndromes Caused by Drug Idiosyncrasy," Osgood, E. E., *J. Am. Med. Assoc.*, 816–18 (1953). A summary made as a report to the Council on Pharmacy and Chemistry of the American Medical Association.

26. "Food Poisoning," Meyer, K. F., *N. Engl. J. Med.*, **249**, 765–73, 804–12, 843–52 (1953), 208 references. An unusually comprehensive critical review of all facets of the subject.

27. "Control of U. S. P. Anti-Anemia Preparation," *J. Am. Med. Assoc.*, **151**, 40–43 (1953), 12 references. A special report of the United States Pharmacopeia Anti-anemia Advisory Board.

28. "Chemotherapy: The Laboratory Assessment of New Drugs," Short, E. I., *J. Pharm. Pharmacol.*, **5**, 217–38 (1953), 132 references. A general and interesting review of the subject.

29. "Bioassays and Mathematics," Gaddum, J. H., *Pharmacol. Revs.*, **5**, 87–134 (1953), 208 references. A summary and critical review of the statistical methods available to pharmacologists in making bioassays.

30. "Industrial Toxicology," Hunter, D., *J. Pharm. Pharmacol.*, **5**, 145–57 (1953), 32 references. Reviews the status of beryllium, cadmium, osmium, and vanadium as well as new highly toxic agricultural chemicals.

PEDIATRICS

1 "Pediatrics," Baty, J. M., Kreidberg, M. B., and Swenson, O., *New Engl. J. Med.*, **247**, 936–42, 977–84 (1952), 166 references. A critical survey of recent developments.

2. "Preventive Prenatal Pediatrics," Ingalls, T. H., *Advances in Pediat.*, **6**, 33–62 (1953), 55 references. A survey of the present status of prenatal disease (prematurity, stillbirth, monstrosities, and congenital anomalies).

3. "Modern Trends in Infant Nutrition and Feeding," Lanman, J. T., *Sugar Research Foundation* (*N. Y.*), *Sci. Rept. Ser.*, *No.* **14**, 1–96 (1952), 184 references. An excellent comprehensive review of the subject.

4. "Management of Breast Feeding," Barnes, G. R., Jr., Lethin, A. N., Jr., Jackson, E. B., and Shea, M. N., *J. Am. Med. Assoc.*, **151**, 192–99 (1953), 11 references. A short practical resume of the subject.

5. "Substitutes for Cow's Milk in Infant Feeding," Glaser, J., *J. Pediat.*, **42**, 734–38 (1953), 26 references. A short critical review.

6. "Infection in the Newborn Baby," Moncrieff, A., *Brit. Med. J.*, **I**, 1–7, (1953), 33 references. A careful complete summary of the subject.

7. "Subdural Effusions in Infancy," Guthkelch, A. N., *Brit. Med. J.*, **I**, 233–39 (1953), 17 references.

8. "Intestinal Obstruction in the Prenatal Period," Koop, C. E., *Advances in Pediat.*, **6**, 63–96 (1953), 47 references. A thorough review of the subject and literature.

9. "Meconium Peritonitis," Bendal, W. L., Jr., and Michel, M. L., Jr., *Surgery*, **34**, 321–33 (1953), 63 references. A review of the literature with a surviving case as background.

10. "Disturbances in Growth," Wilkins, L., *Bull. N. Y. Acad. Med.*, **29**, 280–94 (1953), 9 references. A good concise review for the clinician.

11. "Pediatric Neurology," Baird, H. W., *Progr. Neurol. and Psychiat.*, **8**, 228–38 (1953), 57 references.

12. "A Note on the Etiology of Mongolism," Jervis, G. A., *Quart. Rev. Pediat.*, **8**, 126–30 (1953), 9 references. A review of the well established facts.

13. "Congenital Acromicria (Mongolism) and its Treatment," Benda, C. E., *Quart. Rev. Pediat.*, **8**, 79–96 (1953), 42 references. A review based in part on the author's experience.

14. "Epidemiologic Inferences Derived from Maternal Age," Gordon, J. E., *Am. J. Med. Sci.*, **226**, 326–49 (1953), 202 references. Evidence in the literature supporting maternal age at childbirth as an epidemiologic influence on mass disease in man is carefully covered.

15. "Prophylaxis of Recurrences of Rheumatic Fever with Penicillin Given Orally," Kohn, K. H., Milzer, A., and MacLean, H., *J. Am. Med. Assoc.*, **151**, 347–51 (1953), 12 references. Synopsis of a five years' study.

16. "The Use of Digitalis in Infants and Children," Nadas, A. S., Rudolph, A. M., and Reinhold, J. D. L., *New Engl. J. Med.*, **248**, 98–105 (1953), 42 references. A detailed discussion.

17. "Pink Diseases (Infantile Acrodhynia)," Cheek, D. B., *J. Pediat.*, **42**, 239–60 (1953), 94 references. A comprehensive review on a clinical basis.

18. "The Folic Acid Antagonists in Acute Leukemia of Childhood," Wolman, I. J., Gitbens, J. H., Dickstein, B., Eglick, P. G., Slaughter, B. C., Butson, H. E., and Evans, A. N., *Quart. Rev. Pediat.*, **7**, 121–38 (1952), 18 references. A coverage of the general rules of treatment.

Anesthesia, Shock, and Postoperative Care

1. "Present-Day Concepts of Shock," Frank, H. A., *New Engl. J. Med.*, **249**, 445–53 486–93 (1953), 287 references. A comprehensive review of the subject.

2. "Shock Syndrome," 26 papers by J. Scudder and 38 other authors, *Ann. N. Y. Acad. Sci.*, **55**, 345–542 (1952), 386 references. A symposium devoted to the current status of experimental studies of the shock syndrome and plasma volume expanders.

3. "A Review of Some Recent Advances in the Study of Shock," Eiseman, B., *Surgery*, **33**, 149–60 (1953), 33 references. A critical summary of current knowledge.

4. "Acute Tubular Nephrosis, A Complication of Shock," Moon, V. H., *Ann. Internal Med.*, **38**, 51–60 (1953), 31 references. A brief clear review of the literature.

5. "Hypotensive Anaesthesia in Surgery," Enderby, G. E. H., *Ann. Roy. Coll., Surg. England.* **11**, 310–19 (1952), 6 references. A brief consideration of a recent development.

6. "Review of the Physiology of Dextran," Johnson, E. V., and Lundy,

J. S., *Am. J. Surg.*, **85**, 713–28 (1953), 14 references. An attempt to clarify the mode of action of dextran as a plasma extender.

7. "Special Problems of Pre- and Post-Operative Care," Wylie, W. D., *Ann. Roy. Coll. Surg. England*, 179–89 (1953), 7 references. A consideration of the problems of regurgitation.

DISEASES OF THE RESPIRATORY SYSTEM

1. "Respiratory System," Nielsen, M., and Asmussen, E., *Ann. Rev. Physiol.*, **15**, 85–106 (1953), 178 references. Recent physiology.

2. "The Definition and Assessment of Respiratory Function," Donald, K. W., *Brit. Med. J.*, **I**, 415–22, 473–78 (1953), 66 references. The function of the lungs and methods of its measurement are discussed.

3. "Acclimatization to Low Oxygen Tension," Stickney, J. C., and Van Liere, E. J., *Physiol. Revs.*, **33**, 13–34 (1953), 156 references. For the mammalian and clinical physiologist.

4. "Bronchomotor Tone," Rodbard, S., *Am. J. Med.*, **15**, 356–67 (1953), 74 references. A consideration of a neglected factor in the regulation of the pulmonary circulation.

5. "Electrical Stimulation of Respiration," Bouman, H. D., *Am. J. Physical Med.*, **31**, 40–52 (1953), 37 references. A practical summary of the literature.

6. "Agenesis of the Lung," Oyamada, A., Gasul, B. M., and Holinger, P. H., *Am. J. Diseases Children*, **85**, 182–201 (1953), 155 references. A report of a new case with a review of all previously reported cases.

7. "Antibiotic Therapy in Infections of the Respiratory Tract," Barach, A. L., Bickerman, H. A., and Beck, G. J., *Arch. Internal Med.*, **90**, 808–49 (1953), 90 references. A critical appraisal of the value of antibiotic treatment in chronic bronchial infections.

8. "Acute Respiratory Disease with Special Reference to Pathogenesis, Classification and Diagnosis," Manson, G., *J. Pediat.*, **43**, 599–619 (1953), 60 references. A short review of the recent literature.

9. "Acute Suppurative Bronchopneumonia," Ziskind, M., and Saunders, M., *Am. J. Med. Sci.*, **225**, 81–100 (1953), 116 references. A systematic review of this clinical entity.

10. "Fat Embolism," Glas, W. W., Grekin, T. D., and Musselman, M. M., *Am. J. Surg.*, **85**, 363–69 (1953), 31 references. A review of new data designed to clarify the importance of this diagnosis.

11. "Bronchoesophagology," Putney, F. J., O'Keefe, J. J., McStravog, L. W., and Baltzel, W. H., *Arch. Otolaryngol.*, **58**, 448–94 (1953), 175 references. Summaries of this phase of the otolargynogology literature for 1952.

12. "Advantages and Complications of Tracheotomy," Davis, H. S., Kretchmer, H. E., and Bryce-Smith, R., *J. Am. Med. Assoc.*, **153**, 1156–59 (1953), 13 references. A review of 155 cases.

13. "Thoracic Surgery," Scannell, J. G., *New Engl. J. Med.*, **247**, 800–5,

843–50 (1952), 188 references. A thorough and critical review of the present status of the subject.

14. "Pulmonary Pathology in the Newborn," Potter, E. L., *Advances in Pediat.*, **6**, 157–89 (1953), 42 references. A clinical review.

15. "Mineral Oil Granuloma of the Lungs: An Evaluation of Methods for Identification of Mineral Oil in Tissue," Jampolis, R. W., McDonald, J. R., and Clagett, O. T., *Intern. Abstr. Surg.*, **97**, 105–19 (1953), 100 references. A review of the subject with much attention to a new case which was examined chemically.

16. "Sarcoidosis," Weeden, W. F., and Beckh, W., *Stanford Med. Bull.*, **10**, 39–44 (1952), 24 references. A concise statistical review of 34 new cases.

17. "Penetrating Wounds of the Chest," Farringer, J. L., and Carr, D., *Am. J. Surg.*, **85**, 747–51 (1953), 10 references. A review of 250 cases in civilian life.

MISCELLANEOUS

1. "The Biochemistry of the Teeth," Leicester, H. M., *Ann. Rev. Biochem.*, **22**, 341–50 (1953), 117 references. A summary of the more important recent contributions.

2. "The Surgeon and Ischaemia," Learmonth, J., *Brit. Med., J.*, **I**, 744–48 (1953), 18 references. A very general review.

3. "Thoracoabdominal Incisions," Hart, R. H., *Surgery*, **34**, 773–86 (1953), 36 references. The historical development of thoracoabdominal incisions and the techniques in use today are presented in detail.

4. "Endoscopy," Benedict, E. B., *New Engl. J. Med.*, **248**, 457–64, 500–10 (1953), 132 references. A review of the pertinent literature for the past four years.

5. "Progress in Human Genetics," Kalmus, H., *Biol. Progr.* **2**, 53–77 (1952), 64 references.

6. "Magic, Medicine and Religion," Smith, S., *Brit. Med. J.*, **I**, 848–51 (1953), 4 references. An historical survey.

7. "Ultrasonic Energy as Applied to Medicine," Wakim, K. G., *Am. J. Physical Med.*, **32**, 32–46 (1953), 94 references. A highly critical survey of the present use of sound waves with a frequency of more than 15,000 as applied to medicine.

AUTHOR INDEX

SUBJECT INDEX

vessels; Lungs,
blood vessels
Pulmonary hyaline membrane
see Dyspnea, obstructive
Pulmonary valve
abnormalities
surgical therapy, 401
stenosis, 57
Purienthiol
therapeutic value
in neoplastic conditions,
196
toxicity, 196
Purpura, 87-114
and allergy
etiology and pathogenesis,
176
and coagulation defect, 88,
99-105
definition, 88
diagnostic tests for, 88
fibrinolytic, 88, 105-6
definition, 88
idiopathic thrombocytopenic,
90-95
diagnosis, 90-91
and hormone therapy, 93
immunologic concept, 92
and megakaryocytes, 90,
92, 96
in other fundamental
diseases, 98
and platelet transfusion,
93-94
spleen in, 92
splenectomy, 92-95, 97
thrombocytoasthenia, 90,
94
defined, 90
thrombocytopenic, 89-99
defined, 88
drug induced, 95-96
drugs which induce (list
of), 95-96
neonatal, 96-97
plus hemolytic anemia
and idiopathic-
thrombocytopenic
purpura, 97-98
thrombolytica
see Purpura, fibrinolytic
"thrombotic thrombocyto-
penic", 97
vascular, 98-99
acute, 98-99
etiology, 99
therapy, 99
Pyelonephritis, 78
and heredity, 78
and hypertension, 78

Q

Quinacrine
in lupus erythematosus, 376
Quinidine
and heart disease, 61

R

Radiation-induced
lymphomas
see Lymphomas, radiation
induced
Radiations
biologic effects, 323-38
and causes of death, 324-
27
direct action, 324
dosage, 190
lethal, 325
effects
on blood, 325-27
on teeth, 405-6
indirect action, 324
in neoplastic disease,
190-93
specific, 323-24
Radiations, injuries
aplastic anemia, 324-27
bacteremia, 324-26
hemorrhage, 324-27
lethal, 324-27
modification, 327-30
with anoxia, 327-28
with bone marrow
injections, 328-31
fluids as factor, 330-32
mechanism of, 327, 330
with parabiosis, 328-30
postradiation procedures,
328-32
with spleen shielding
technique, 169, 328-29
and splenectomy, 330-31
and splenic tissue
suspensions, 328-31
Radioactivity, 323-38
reviews in, annotated,
440-42
Radiogold
dosage, 192
in malignancies, 191-92
and teeth, 406
Radioiodine, 191
and cortisone
in thyroid, 137
in diabetes insipidus with
hyperthyroidism, 131
dosage, 152
and growth hormone, 117
in hyperthyroidism, 151-
52
and hypopituitarism,
124-25
and pancreatitis, 46
Radiology
reviews in, annotated,
440-42
Radiophosphorus
and teeth, 406
Radiosensitivity
of various tissues, 190
Radiothyroxin

experiments, 149
Regitine
in diagnosis of pheochromo-
cytoma, 145-46
effects, 63
Reproductive system,
diseases
reviews in, annotated,
439-40
Resins
exchange
and heart disease, 61
Respiration
biochemistry of, 259
Respiratory circulation
in cardiovascular disease,
242
in lung disease, 240,
242-44
Respiratory gases
determination of
method of Bohr, 269-70
method of Filley, 269,
272-73
method of Krogh, 269-71
method of Lilienthal,
271-72
diffusing capacity
applications, 273-78
concepts and methods,
268-73
measurements, 276-77
in normal subjects, 273-
74
opportunities for experi-
mentation, 277
in pulmonary disease,
274-78
in subjects with mitral
stenosis, 275-76
diffusion, 267-78
definition, 268
Respiratory system
and allergies, 174-75, 177
diseases, 28, 237-84
reviews in, annotated,
447-48
nalorphine stimulation,
317-18
Reticuloendothelial system
diseases, 87-114
reviews in, annotated,
424-26
Retrolental fibroplasia
etiology and pathogenesis,
395-96
Rh factor
and allergies, 169
and congenital abnormali-
ties, 391
Rheumatic fever
cardiac complications,
57-58
diagnosis, 58
therapy, 57-58
and streptococci, 17
treatment, 17